ublished by the American Medical Association

January 1989
Volume 143, Number 1

Acc 1.3.89
CUK-H01330-10-P02424

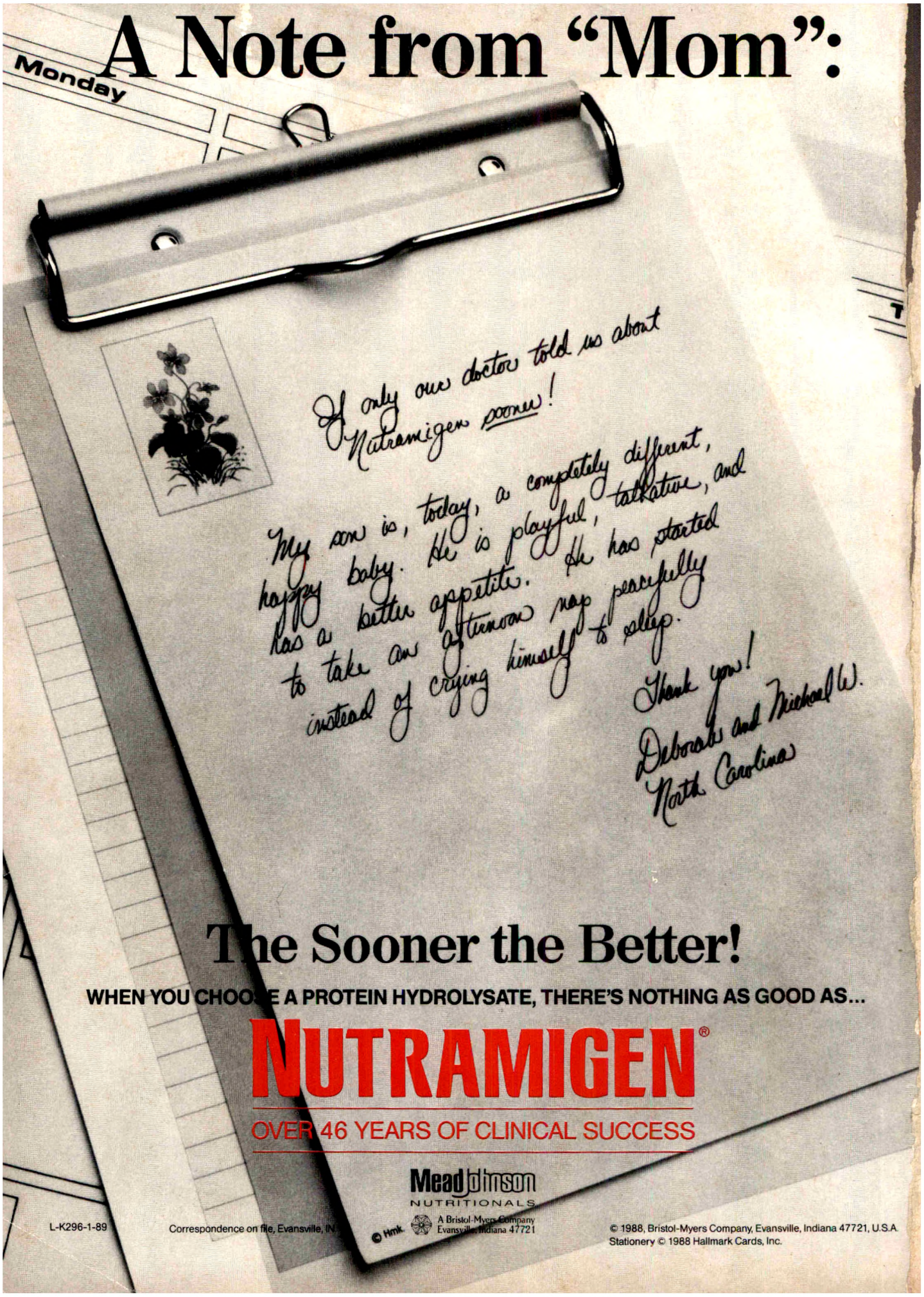
AJDC

AMERICAN JOURNAL OF DISEASES OF CHILDREN

10

THE PEDIATRIC FORUM		9
LIST OF 1988 REVIEWERS FOR *AJDC*		21
THE EDITORIAL BOARD SPEAKS . . . : Advances in Pediatric Cardiology	*B. C. Morgan*	24
ARTICLES: Passive Inhalation of Cocaine by Children	*D. A. Bateman et al*	25
Immunogenetics of *Haemophilus* B Vaccine	*K. P. Ramsey et al*	28
Immunization After HIB Infection	*K. M. Edwards et al*	31
Epidemic Neonatal *S aureus* Infections	*A. C. Reboli et al*	34
REVIEW: Neonatal Neutrophil Host Defense	*M. S. Cairo*	40
ARTICLES: Enzyme Immunoassay in Adolescent *Chlamydia* Infection	*K. Soren et al*	51
Compliance in Adolescents With Iron Deficiency	*B. A. Cromer et al*	55
Household Electrical Injuries	*M. D. Baker et al*	59
Intrauterine and Postnatal Brain Growth	*M. Hack et al*	63
PEDIATRIC PERSPECTIVES: The Pediatrician as a Consultant	*G. B. Stickler*	73
ARTICLES: Congenital Velopharyngeal Insufficiency	*D. G. Durr et al*	75
Pulmonary Function After IV Indomethacin	*A. N. Krauss et al*	78
Nutrition in Very-Low-Birth-Weight Infants	*M. K. Georgieff et al*	82
Reported Sexual Behaviors and Self-esteem Among Young Adolescents	*D. P. Orr et al*	86
SPECIAL FEATURES: Radiological Cases of the Month	*C. A. Bullaboy et al* *A. K. Pramanik et al*	93 95
ARTICLES: Safety of Early Newborn Discharge	*P. D. Conrad et al*	98
Diagnosis of GABHS Pharyngitis in the Office	*B. Taubman et al*	102
ECG Failure in Cardiac Arrest	*J. R. Brownlee et al*	105
Single Umbilical Artery	*A. K. C. Leung*	108
Health Status of Children in Self-care	*R. L. Williams et al*	112
Diagnosis of Male Delayed Puberty	*P. B. Kaplowitz*	116
Reprint Requests	*A. K. C. Leung*	121
LEADS FROM THE MMWR		125

A Note from "Mom":



The Sooner the Better!

WHEN YOU CHOOSE A PROTEIN HYDROLYSATE, THERE'S NOTHING AS GOOD AS...

NUTRAMIGEN®

OVER 46 YEARS OF CLINICAL SUCCESS

Mead Johnson NUTRITIONALS

A Bristol-Myers Company
Evansville, Indiana 47721

L-K296-1-89

Correspondence on file, Evansville, IN

© Hmk.

© 1988, Bristol-Myers Company, Evansville, Indiana 47721, U.S.A.
Stationery © 1988 Hallmark Cards, Inc.

Vol. 143

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOL 143 NO. 1 JANUARY 1989

Copyright © 1989 by the American Medical Association

THE PEDIATRIC FORUM

9 ***Haemophilus influenzae* Type e (Biotype IV) Meningitis** Gary S. Marshall, MD, Karin L. McGowan, PhD, Philadelphia . . . **Why Are There No Educators With PhD Degrees in Pediatric Departments?** Larrie W. Greenberg, MD, Washington, DC . . . **PhD Faculty in the Clinical Department** Glenn J. Gormley, MD, PhD, Westfield, NJ . . . **Discretion Advised When Lowering the Serum Lipid Levels of Children** Mary E. Kazanecki; Mona F. Melhem, MD; K. N. Rao, PhD, Pittsburgh . . . **Ectrodactyly, Ectodermal Dysplasia, and Clefting Associated With Thymic Aplasia** Meenakshi Jhaveri, MD; Scott H. Barnett, MD; Melvin Gertner, MD; Yong-Myun Rho, MD; Joseph C. Segen, MD, Elmhurst, NY

21 **LIST OF 1988 REVIEWERS FOR *AJDC***

THE EDITORIAL BOARD SPEAKS . . .

24 **Advances in Pediatric Cardiology**
Beverly C. Morgan, MD, Orange, Calif

ARTICLES

25 **Passive Freebase Cocaine ('Crack') Inhalation by Infants and Toddlers**
David A. Bateman, MD, Margaret C. Heagarty, MD, New York

28 ***Haemophilus* B Polysaccharide Vaccine**
CPT Keith P. Ramsey, MC, USA; COL Lou A. Popejoy, MC, USA; CPT Steven W. Jesse, MC, USA; CPT Ines Gonzales-Torres, MC, USA, El Paso, Tex

31 **Immunization After Invasive *Haemophilus influenzae* Type b Disease**
Kathryn M. Edwards, MD; Michael D. Decker, MD, MPH; Carol R. Porch, MD; Pamela Palmer, MS; Roberta Bradley, MSN, Nashville, Tenn

34 **Epidemic Methicillin-Gentamicin–Resistant *Staphylococcus aureus* in a Neonatal Intensive Care Unit**
Annette C. Reboli, MD; Joseph F. John, Jr, MD; Abner H. Levkoff, MD, Charleston, SC

REVIEW

40 **Neonatal Neutrophil Host Defense**
Mitchell S. Cairo, MD, Irvine, Calif

ARTICLES

51 ***Chlamydia* and the Adolescent Girl**
Karen Soren, MD, Earnestine Willis, MD, MPH, Chicago

55 **Psychosocial Determinants of Compliance in Adolescents With Iron Deficiency**
Barbara A. Cromer, MD; Karl Steinberg, MD; Lynne Gardner, RD, MPH; David Thornton, PhD; Barry Shannon, PhD, Columbus, Ohio

59 **Household Electrical Injuries in Children**
M. Douglas Baker, MD, Philadelphia, Christine Chiaviello, MD, Baltimore

63 **Differential Effects of Intrauterine and Postnatal Brain Growth Failure in Infants of Very Low Birth Weight**
Maureen Hack, MB, ChB; Naomi Breslau, PhD; Avroy A. Fanaroff, FRCPE, DCH, Cleveland

Continued on p 3.

P 24,241

UNIVERSITY COLLEGE OF MEDICINE LIBRARY

Monthly Circulation >44 500
Also published in French

EDITORIAL BOARD

Editor

Vincent A. Fulginiti, MD
American Journal of Diseases of Children
PO Box 43700
Tucson, AZ 85733
(602) 626-4304

Associate Editors

James J. Corrigan, Jr, MD
Tucson

Alan D. Bedrick, MD
Tucson

Book Review Editor

Peggy C. Ferry, MD
Tucson

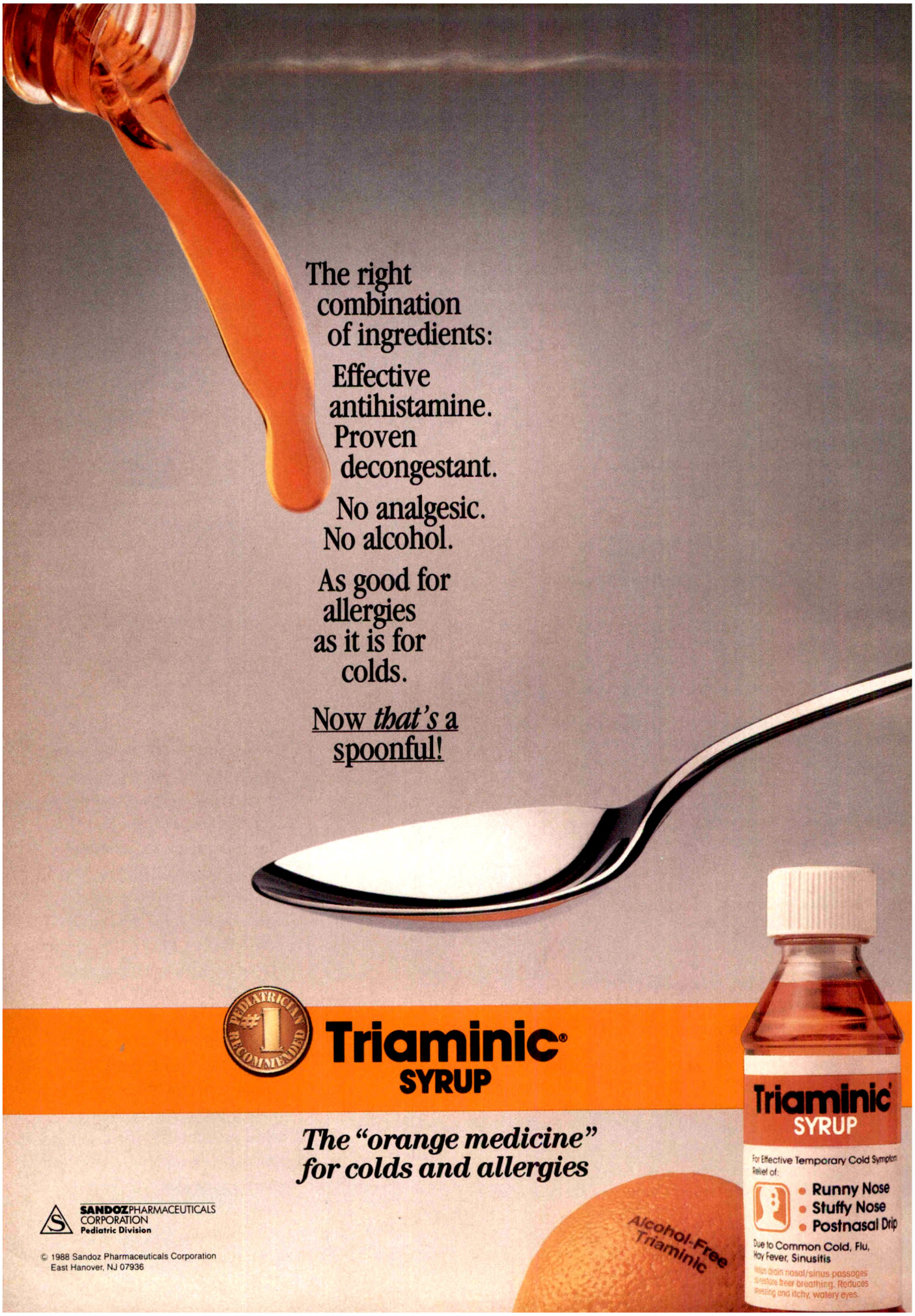
Administrative Assistant

Joann M. Quane
Tucson

Secretary

Laura Martin
Tucson

Hugh D. Allen, MD, Columbus, Ohio
Milton I. Arnold, MD, Los Angeles
Richard W. Blumberg, MD, Atlanta
Ben H. Brouhard, MD, Cleveland
George W. Brown, MD, Los Lunas, NM
Beverly B. Dahms, MD, Cleveland
Murray Feingold, MD, Boston
Patricia Ferrieri, MD, Minneapolis
Laurence Finberg, MD, Brooklyn, NY
Boyd W. Goetzman, MD, PhD, Davis, Calif
John D. Johnson, MD, Albuquerque
James P. Keating, MD, St Louis
Elizabeth R. McAnarney, MD, Rochester, NY
Dan G. McNamara, MD, Houston
Beverly C. Morgan, MD, Orange, Calif
Henry L. Nadler, MD, Chicago
Robert Penny, MD, Los Angeles
Albert W. Pruitt, MD, Augusta, Ga
Kenneth B. Roberts, MD, Worcester, Mass
Barton D. Schmitt, MD, Denver
E. Richard Stiehm, MD, Los Angeles
William B. Strong, MD, Augusta, Ga
Beverly P. Wood, MD, Rochester, NY


The right combination of ingredients:
Effective antihistamine.
Proven decongestant.
No analgesic.
No alcohol.
As good for allergies as it is for colds.
Now that's a spoonful!
#1 PEDIATRICIAN RECOMMENDED
Triaminic®
SYRUP
The "orange medicine" for colds and allergies
Triaminic
SYRUP
For Effective Temporary Cold Symptom Relief of:
Runny Nose
Stuffy Nose
Postnasal Drip
Due to Common Cold, Flu, Hay Fever, Sinusitis
Helps drain nasal/sinus passages to restore freer breathing. Reduces sneezing and itchy, watery eyes.
Alcohol-Free Triaminic
SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division
© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

Continued from p 1.

PEDIATRIC PERSPECTIVES

73 The Pediatrician as a Consultant
Gunnar B. Stickler, MD, Rochester, Minn

ARTICLES

75 Otologic Manifestations in Congenital Velopharyngeal Insufficiency
Dory G. Durr, MD, FRCSC,
Robert S. Shapiro, MD, CM, FRCSC, Montreal

78 Pulmonary Function in Preterm Infants Following Treatment With Intravenous Indomethacin
Alfred N. Krauss, MD; Nunzia Fatica, MD; Barbara S. Lewis, MD;
Rebecca Cooper, MD; Howard T. Thaler, PhD;
Constance Cirrincione, MS; John O'Loughlin, MD; Aaron Levin, MD;
Mary Allen Engle, MD; Peter A. M. Auld, MD, New York

82 Changes in Nutritional Management and Outcome of Very-Low-Birth-Weight Infants
Michael K. Georgieff, MD; Marla M. Mills, RN; Linda Lindeke, PNP;
Sandra Iverson, PNP; Dana E. Johnson, MD, PhD;
Theodore R. Thompson, MD, Minneapolis

86 Reported Sexual Behaviors and Self-esteem Among Young Adolescents
Donald P. Orr, MD; Mary L. Wilbrandt, MSW; Catherine J. Brack, MS;
Steven P. Rauch, MSW; Gary M. Ingersoll, PhD, Indianapolis

SPECIAL FEATURES

93 Radiological Cases of the Month
Charles A. Bullaboy, MD; Rufus B. Jennings, Jr, MD;
David H. Johnson, MD; John D. Coulson, MD (*Contributors*), Norfolk, Va;
Lionel W. Young, MD (*Editor for This Case*), Akron, Ohio;
Beverly P. Wood, MD (*Section Editor*),Rochester, NY;

95 Arun K. Pramanik, MD, Sarita Sharma, MD (*Contributors*), Shreveport, La;
Beverly P. Wood, MD (*Section Editor*), Rochester, NY

ARTICLES

98 Safety of Newborn Discharge in Less Than 36 Hours in an Indigent Population
Paul D. Conrad, MD; Randall B. Wilkening, MD;
Adam A. Rosenberg, MD, Denver

102 The Diagnosis of Group A, β-Hemolytic Streptococcal Pharyngitis in the Office Setting
Bruce Taubman, MD, Philadelphia;
Robert P. Barroway, MD, Cherry Hill, NJ;
Karin L. McGowan, PhD, Philadelphia

Continued on p 4.

The AMERICAN JOURNAL OF DISEASES OF CHILDREN is a member of the consortium of AMA journals listed below. The Archives reaches more than 41 500 readers in 85 countries each month. The complete text of all AMA journals is available on the MEDIS data base from Mead Data Central, Dayton, Ohio.

JAMA The Journal of the American Medical Association

AJDC American Journal of Diseases of Children

archives of
Dermatology

archives of
General Psychiatry

archives of
Internal Medicine

archives of
Neurology

archives of
Ophthalmology

archives of
Otolaryngology-Head & Neck Surgery

archives of
Pathology & Laboratory Medicine

archives of
Surgery

James H. Sammons, MD, Executive Vice-President

James S. Todd, MD, Senior Deputy Executive Vice-President

Kenneth E. Monroe, Deputy Executive Vice-President

Theodore R. Chilcoat, Jr, Assistant Executive Vice-President

M. Roy Schwarz, MD, Assistant Executive Vice-President

George D. Lundberg, MD, Vice-President, Scientific Information

John T. Baker, Vice-President, Publishing

Norman D. Richey, Director, Publication Production and Printing Division

Lee A. Parent, Director, Circulation-Fulfillment Division

Dennis Joseph Dennehy, Director, Advertising Sales and Promotion Services Division

Thomas J. Carroll, Director, Department of Advertising Communication

Raymond Christian, Director, Advertising Services Department

PUBLICATION STAFF
Offices: 535 N Dearborn St,
Chicago, IL 60610

Managing Editor and Director, AMA Specialty Journals:
Michael D. Springer

Associate Editor:
Julie Foreman

Production Manager:
Marlene M. Hinsch

Assistant Production Manager:
John R. Sayban

Editorial Processing Manager:
Cheryl Iverson

Assistant Editorial Processing Manager:
Paula Glitman

Permissions and Graphic Design Manager:
Dennis J. Shipley

Staff Assistants:
Diane Darnell
Bonnie Van Cleven

Copy Editing:
Patricia A. Predey (Supervisor)
Vickey Golden (Free-lance Coordinator)
Paul Frank (Senior Copy Editor)
Stephen Borysewicz
John Radanovich

Production Supervisors:
Betty Frigerio (Advertising)
Thomas J. Handrigan (Illustrations)
Elizabeth Petrikenas (Proofreading)
Mary C. Steermann (Editorial)
JoAnne Weiskopf (Layout)

Proofreading:
Teresa H. Omiotek
Jennifer Reiling
Richard T. Porter
Barbara Wojtowicz

Art and Senior Production Assistants:
Melinda Arcabos
Debra Lucas
Cari Biamonte
Kimberly McCormick
Laura Bleiler
Juliana K. Mills
Karen Branham
Dorothy Patterson
Cynthia Gelper
Susan Price
Jerri Hall-Gortowski
E. Ruth White
Anita Henderson
Ellen Yoshihara
Sally Hoyt

Production Assistant:
Darlene E. Filips

Editorial Assistant:
Jean Schaffner

Department of Scientific and Socioeconomic Indexing:
Norman Frankel (Director)
George Kruto
Mary Kay Tinerella
Susan McClelland

Please address communications concerning accepted or published communications to AMA Specialty Journals, 535 N Dearborn St, Chicago, IL 60610.

EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

Continued from p 3.

105 Failure of Electrocardiographic Monitoring to Detect Cardiac Arrest in Patients With Pacemakers
John R. Brownlee, MD; Gerald A. Serwer, MD; Macdonald Dick II, MD; Thomas Bauld, PhD; Amnon Rosenthal, MD, Ann Arbor, Mich

108 Single Umbilical Artery
Alexander K. C. Leung, MBBS, FRCPC, MRCP(UK), MRCPI, William Lane M. Robson, MD, FRCPC, Calgary, Alberta

112 Health Status of Children in Self-care
Rickey L. Williams, MD, Tucson, W. Thomas Boyce, MD, San Francisco

116 Diagnostic Value of Testosterone Therapy in Boys With Delayed Puberty
Paul B. Kaplowitz, MD, PhD, Richmond, Va

121 Reprint Requests
Alexander K. C. Leung, MBBS, FRCPC, FAAP, MRCP(UK), MRCPI, Calgary, Alberta

125 LEADS FROM THE MMWR

BOOK REVIEWS

Diagnostic Imaging in Paediatrics (Gordon, ed) Reviewed by Beverly P. W MD, Rochester, NY (p 27) . . . **Pediatric Cerebrovascular Disorders** (R Riela) Reviewed by Robert C. Vannucci, MD, Hershey, Pa (p 107) . . . **Paedi Trauma** (Alpar, Owens) Reviewed by Martha Bushore, MD, West Palm Be Fla (p 115)

7 INSTRUCTIONS FOR AUTHORS

14 INDEX TO ADVERTISERS

AJDC, American Journal of Diseases of Children (ISSN 0002-922X) is published mont American Medical Association, 535 N Dearborn St, Chicago, IL 60610, and is an official pub the Association. Second-class postage paid at Chicago and at additional mailing office.

SUBSCRIPTION RATES—The subscription rates for the American Journal of Diseases o are as follows: $48 for one year, $81 for two years in the United States and US Possession countries, one year, $58; two years, $101 for surface delivery. (For expedited air deliver countries, add $15 surcharge for one year subscription, $30 for two years.) Rates for subscr delivery to Japan or South Korea are available through exclusive agents—contact the ***Special rates for residents and medical students in the United States and US Posses available.*** Address inquiries to the American Medical Association, Circulation and Fulfillmen 535 N Dearborn St, Chicago, IL 60610. Phone: (312) 280-7168.

CHANGE OF ADDRESS—POSTMASTER, send all address changes for AJDC, American Diseases of Children to Caryl L. Wertheimer, Director of Fulfillment, 535 N Dearborn St, C 60610. Notification of address change must be made at least six weeks in advance, includ and new addresses, a recent mailing label, and your new zip code.

ADVERTISING OFFICES: Eastern: 600 Third Ave, Suite 3700, New York, NY 10016 (Robert C. Corcoran [212-867-6640]; **Representative:** Phillip B. Altamore); **Midwest/Farwe** Dearborn St, Chicago, IL 60610 (**Manager:** Thomas J. Carroll [312-280-7182]; **Representati** P. Cahill, Midwest; Daniel T. Mjölsness, Farwest)

Advertising Principles: Each advertisement in this issue has been reviewed and complie principles governing advertising in AMA scientific publications. A copy of these principles is on request. The appearance of advertising in AMA publications is not an AMA guarantee or en of the product or the claims made for the product by the manufacturer.

When I was a child there was no Orimune®

Poliovirus Vaccine Live, Oral Trivalent

Jackie DiLorenzo of Hastings-on-Hudson, New York, contracted polio in 1950, before a vaccine became available. She spent ten years in rehabilitation, during which time she underwent nine operations on her spine, legs and feet. Jackie currently lives in a house adapted for wheelchair living.

Lederle Biologicals Protecting Families Through Immunization®

Please see following page for brief summary of prescribing information.

When I was a child there was no Orimune®

Proven in Millions of US Patients

ORIMUNE was the first live, oral, trivalent polio vaccine. No other oral polio vaccine has done more to help eradicate wild poliovirus in the US. Approximately 500 million doses have been distributed to date.

Proven Safety Record*

Lederle takes every precaution during production and testing to ensure the safety of ORIMUNE. This dedication is evident by our 25-year safety record.

Uninterrupted Supply

Lederle has consistently met the nation's needs for oral polio vaccine for about 25 years. In fact, when all other US manufacturers discontinued the production of oral polio vaccine, Lederle has remained committed to this essential product and to the health of America's children.

Available in Single-Doses

ORIMUNE is available in convenient, unit-dose DISPETTES® to help assure dosage accuracy and avoid the risk of contamination.

*See adverse reactions section of brief summary

Orimune®
Poliovirus Vaccine Live, Oral Trivalent

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

A Brief Summary

Please see package insert for full description, directions for use, and references.

INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*
CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must* not be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must* not be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev. 8/86

Lederle Biologicals
Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470
© 1988 Lederle Laboratories
603-8

Instructions for Authors

NEW MANUSCRIPT PROCEDURE

On Jan 1, 1988, *AJDC* initiated a new procedure. Manuscripts submitted to *AJDC* will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information.—Please send manuscripts and correspondence by first-class mail (*do not use registered, certified, or express mail*) to the Editor, Vincent A. Fulginiti, MD, *AJDC*, PO Box 43700, Tucson, AZ 85733. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval *if requested* by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

Step 1.—*Cover Letter.*—All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNATURES):

1. *Copyright Release.*—"In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA."

2. *Statement of Affirmation.*—"This manuscript has not been published anywhere in any language and is not under simultaneous consideration by another publication. This manuscript is original and ALL authors have seen and approve of its contents."

3. *Financial Disclosure.*—List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg, employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of *AJDC*.

Step 2.—*Manuscript Format.*—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. *Do not use justified right margins.*

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with *each line, including headings, double-spaced*. Continuations should be on a second sheet with all headings repeated.

9. Use Système International (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed *label* and affixed on the back of each illustration. *Do not write directly on the print.*

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transparencies, mounted in cardboard and carefully [illegible] mounted transparencies or color prints. Fee is $400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from *both* parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, et al: Persistent fetal circulation: Neurodevelopment outcome. *AJDC* 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P: Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty, in Conly J, Dickinson JT (eds): *Plastic and Reconstructive Surgery of the Face and Neck*. New York, Grune & Stratton, 1972, pp 84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.

13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from *publisher* and *author*. Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3.—*Special Departments.*—Criteria for several special departments are given below.

1. *The Pediatric Forum.*—This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. *From Research to Relevance.*—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. *Educational Interventions.*—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

4. *Sports Medicine.*—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
- ____ 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors.
- ____ 3. Original typed manuscript plus three copies.
- ____ 4. Triple-spacing; double-spacing for tables and legends.
- ____ 5. Right margins UNJUSTIFIED.
- ____ 6. Title 75 characters or less.
- ____ 7. Abstract included.
- ____ 8. References in proper format, cited in numerical order.
- ____ 9. Four sets of illustrations.
- ____ 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- ____ 12. Permission forms for illustrations previously published elsewhere.

ow, MDI therapy s available to more patients han ever before

New AeroChamber®
WITH *MASK* (aerosol holding chamber)

rmits easier metered-dose-inhaler (MDI) therapy in chil-en and the elderly (see boxed statement below). The device nsists of an aerosol holding chamber with a soft, flexible mask that vers the patient's nose and mouth. A one-way valve holds the medica-n until the patient inhales. Expired air is vented through exhalation rts. AeroChamber with *Mask* is economical and fits virtually any inhaler.

IMPORTANT INFORMATION
Package insert dosing instructions should be consulted for all metered dose inhalers (MDIs) when used with AeroChamber with *Mask*.
Dosage and administration recommendations vary for different MDIs, and the limitations and conditions of use for each product should be considered before utilizing this device, particularly for younger and older patients.

☐ **Yes, I am interested in the New AeroChamber® with *Mask*. Please send more information.**

AJDC 1/89

☐ **Enclosed is my check or money order for:**

#Units		Price		Total
_____	×	**$22.00**	=	_____

Minimum order—6 units. Price includes postage and handling.

me _____
(please print)
dress _____
_____
te _____ Zip _____
one ( ) _____

p and mail to: **AeroChamber® with *Mask***
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

r more information or to place an order now, call 1-800-325-1605.

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

988 Forest Pharmaceuticals, Inc.

AWM-008-88

ACADEMIC PEDIATRIC CARDIOLOGIST

The Department of Pediatrics, East Carolina University School of Medicine is seeking a 4th BC/BE Pediatric Cardiologist to join a rapidly growing and busy section of pediatric cardiology.

An interest in invasive cardiology is preferred but not required. Responsibilities include patient care, teaching and clinical or laboratory research. Faculty rank and salary will be commensurate with training and experience.

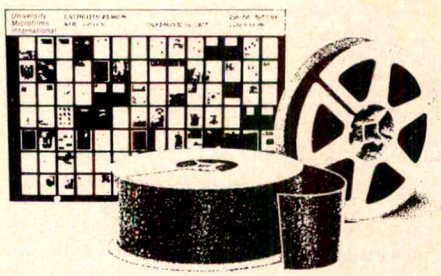
Send letter of inquiry and CV to **J. Peter Harris, M.D., Section of Pediatric Cardiology, Dept. of Pediatrics, East Carolina University School of Medicine, Greenville, North Carolina 27858-4354.**

East Carolina University

Federal law requires proper documentation of identity and employability at the time of employment. It is requested this documentation be included with your application.

East Carolina University is an AA / EEO Employer and encourages applications from qualified women and minorities.

this publication is available in microform



Please send me additional information.

University Microfilms International

300 North Zeeb Road
Dept. P.R.
Ann Arbor, MI 48106
U.S.A.

18 Bedford Row
Dept. P.R.
London, WC1R 4EJ
England

Name _____
Institution _____
Street _____
City _____
State _____ Zip _____

The Pediatric Forum

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

Haemophilus influenzae Type e (Biotype IV) Meningitis

Sir:—Invasive disease due to encapsulated, non–type b strains of *Haemophilus influenzae* is rare despite the fact that nasopharyngeal carriage of such strains is comparable to that of type b organisms.[1] Some serious non–type b infections occur in immunologically or anatomically impaired hosts, while others occur in apparently normal individuals.[2,3] Whereas the absolute incidence of such infections should be unaffected by the introduction and widespread use of type b capsular polysaccharide vaccines, their relative importance may increase, as has been suggested.[2] This report of *H influenzae* type e meningitis in an infant and the accompanying literature review delineate a pathogenic role for this organism in normal hosts and emphasize an association with taxonomic biotype IV.

Patient Report.—A 3-month-old male infant presented with a 36-hour history of intermittent fever to temperature as high as 39.4°C, irritability, poor feeding, and vomiting. He was the 2.5-kg product of a 38-week twin gestation whose neonatal course was complicated only by transient tachypnea. His subsequent healthy history was unremarkable; he had received one diphtheria, tetanus, and pertussis–oral polio vaccination without incident and suffered a mild episode of bronchiolitis at 10 weeks of age. The family history was negative for immunodeficiency. Physical examination revealed a poorly perfused, irritable baby with nuchal rigidity and a bulging anterior fontanelle. The cerebrospinal fluid (CSF) contained 10.5×10^9/L white blood cells (0.92 segmented neutrophils) and 576×10^6/L red blood cells; the protein concentration was 1.66 g/L, and the glucose level was 1.4 mmol/L (serum glucose, 8.9 mmol/L). *Haemophilus influenzae* grew from a CSF culture; it was determined to be type e by slide agglutination (Difco Laboratories, Detroit), β-lactamase negative by the chromogenic cephalosporin technique, and susceptible to ampicillin and chloramphenicol, with minimal inhibitory concentrations of ≤1.0 mg/L and ≤8.0 mg/L, respectively. The isolate was further characterized as biotype IV because there was ornithine decarboxylase and urease activity in the absence of indole production.[4]

Empiric antibiotic treatment with ampicillin sodium and cefotaxime sodium resulted in rapid improvement. Administration of cefotaxime was discontinued on the second hospital day, and by the third day the patient was afebrile. A repeated CSF examination at that time revealed 1.9×10^9/L white blood cells (0.78 segmented neutrophils), 110×10^6/L red blood cells, a protein concentration of 0.87 g/L, and a glucose concentration of 2.4 mmol/L. Culture of CSF was negative, as was a urine latex agglutination test for type b polysaccharide antigen (Wampole Laboratories, Cranbury, NJ). By hospital day 4 he was alert, active, playful, and feeding well. Ampicillin treatment was continued for a total of ten days. At discharge he was free from detectable neurologic abnormalities, and at this writing he remains healthy and developmentally equivalent to his twin brother.

Comment.—We have found reference to nine previous cases of meningitis due to *H influenzae* type e[3,5-12]; clinical details were provided for only five of these cases and are summarized in the Table. All of these cases were reported after 1975 and all occurred in children, only one of whom had a reported predisposing condition (a CSF leak). Review of these cases reveals clinical features indistinguishable from typical *H influenzae* type b meningitis. The paucity of reported meningitis cases is in accord with our recent experience with invasive *H influenzae* disease; no type e isolates were recorded among blood culture results at our institution from 1977 through 1987, a period during which *H influenzae* bacteremia was diagnosed in approximately 450 children.

It appears that all type e isolates thus far analyzed, including one that caused bacteremia in an adult,[13] belong to biotype IV, whereas the more invasive capsular type b organism is usually biotype I.[12,14,15] This is particularly

Meningitis due to *Haemophilus influenzae* Type e*

Source, y	Country	Patient Age/Sex	Underlying Condition	Ampicillin Susceptible	Biotype	Outcome
Present study, 1988	US	3 mo/M	NR	Yes	IV	Good
Gilsdorf,[3] 1987	US	6 y/F	CSF leak	No†	NR	Survived
Controni et al,[11] 1982	US	8 y/M	NR	Yes	IV	Good
Shishido and Matsumoto,[10] 1979	Japan	16 mo/F	NR	Yes	IV	Good
Hodes and Leidy,[9] 1977	US	4 mo/M	NR	Yes	NR	Good
Buck and Douglas,[8] 1976	US	8 mo/F	NR	Yes	NR	Survived

*NR indicates not reported.
†β-Lactamase positive.

interesting in that biotype IV is disproportionately represented among nontypable isolates that cause neonatal sepsis, as opposed to those recovered from mucosal surfaces, which are usually biotype II or III.[16] The pathogenetic significance of taxonomic biochemical types at this point is unclear and requires further study.

There are data to suggest that nontype b polysaccharide capsules render *H influenzae* strains more susceptible to the antibody-independent action of complement; therefore, natural immunity to invasive disease may exist in the absence of specific antibody.[17] The above recent experience with invasive type e disease is difficult to explain in light of this. Our case and a literature review confirm that *H influenzae* type e is a cause of typical bacterial meningitis in the normal pediatric host. Clinicians need to be alerted to this, particularly since it represents a potential pitfall in the use of type b antigen–specific latex agglutination tests for the rapid diagnosis of serious *H influenzae* infections.

GARY S. MARSHALL, MD
KARIN L. MCGOWAN, PHD
Division of Infectious Diseases
The Children's Hospital
of Philadelphia
34th Street and
Civic Center Boulevard
Philadelphia, PA 19104

1. Dawson B, Zimmerman K: Incidence and type distribution of *Haemophilus influenzae* strains. *Br Med J* 1952;1:740-742.
2. Greene GR: Meningitis due to *Haemophilus influenzae* other than type b: Case report and review. *Pediatrics* 1978;62:1021-1025.
3. Gilsdorf JR: *Haemophilus influenzae* nontype b infections in children. *AJDC* 1987;141: 1063-1065.
4. Kilian M: A taxonomic study of the genus *Haemophilus*, with the proposal of a new species. *J Gen Microbiol* 1976;93:9-62.
5. Platt AE: Serological study of *Haemophilus influenzae*. *J Hyg* 1937;37:98-107.
6. Omland T: Serological studies on *Haemophilus influenzae* and related species: II. Examination of the type specific antigens of *H influenzae* by means of the capsular swelling method. *Acta Pathol Microbiol Scand* 1963;57: 279-285.
7. Todd JK, Bruhn FW: Severe *Haemophilus influenzae* infections: Spectrum of disease. *AJDC* 1975;129:607.
8. Buck LL, Douglas GW: Meningitis due to *Haemophilus influenzae* type e. *J Clin Microbiol* 1976;4:381.
9. Hodes DS, Leidy G: Meningitis caused by *Haemophilus influenzae* type e. *J Pediatr* 1977; 91:844.
10. Shishido H, Matsumoto K: Meningitis due to *Haemophilus influenzae* type e biotype 4. *J Clin Microbiol* 1979;10:926-927.
11. Controni G, Rodriguez WJ, Chang MJ: Meningitis caused by *Haemophilus influenzae* type e, biotype 4. *South Med J* 1982;75:78.
12. Albritton WL, Penner S, Slaney L, et al: Biochemical characteristics of *Haemophilus influenzae* in relationship to source of isolation and antibiotic resistance. *J Clin Microbiol* 1978;7: 519-523.
13. Cawthern TH, Marraro RV, McCleskey FK: Bacteremia associated with *Haemophilus influenzae* type e biotype 4. *J Clin Microbiol* 1978;7:1-2.
14. Oberhofer TR, Back AE: Biotypes of *Haemophilus* encountered in clinical laboratories. *J Clin Microbiol* 1979;10:168-174.
15. Kamme C: Biotypes of capsulated and noncapsulated *Haemophilus influenzae:* Correlation between biotypes and beta-lactamase production. *Acta Pathol Microbiol Scand* 1980;88:261-264.
16. Wallace RJ Jr, Baker CJ, Quinones FJ, et al: Nontypable *Haemophilus influenzae* (biotype 4) as a neonatal, maternal, and genital pathogen. *Rev Infect Dis* 1983;5:123-136.
17. Sutton A, Schneerson R, Kendall-Morris S, et al: Differential complement resistance mediates virulence of *Haemophilus influenzae* type b. *Infect Immun* 1982;35:95-104.

Why Are There No Educators With PhD Degrees in Pediatric Departments?

Sir:—The survey results on PhD degrees in academic pediatric departments as reported by Leuschen et al[1] in addition to the provocative commentaries by Drs Morrow[2] and Fulginiti[3] were fascinating and warrant some further observations and commentary. The authors pointed out the major issues chairmen face when they consider hiring a faculty member with a PhD degree for their departments; ie, criteria for promotion and tenure, salary considerations, and departmental expectations. The survey indicated those subspecialty areas with which faculty members with PhD degrees are primarily affiliated, and there was no mention of educator/researchers with EdD degrees working with chairmen, training program directors, or student clerkship coordinators.

The General Professional Education of the Physician (GPEP) report[4] has provided the stimulus in this country for departments and medical schools to examine their approaches toward medical education and to initiate change. However, few physicians receive formal training in medical education, and perhaps it is a sign of the status quo that not one pediatric department of those surveyed reported employing a trained educator (although I was aware of at least three such relationships in 1986). It is possible that pediatric departments have sought and are receiving educational assistance from the offices of research in medical education within their affiliated medical schools.[5] However, there appears to be minimal interchange between the two, as evidenced by the paucity of collaborative research and programs reported in the pediatric and medical education literature and at national meetings.

Because training program directors and clerkship coordinators are not only pressured to orchestrate successful programs with limited resources but are also expected to teach and publish to advance academically, chairmen should be willing to consider investing in an educator who will work in concert with clinicians to decompress this situation and help provide a better education to students and residents. The model I am proposing, ie, employing an individual who will share responsibility for educational planning and evaluation in the department, will not pay for itself but represents a sound investment and will not be a financial burden to the department. The returns should be measured in new and/or improved programs, improved teaching, and more effective evaluation, not in dollars.

Having been associated with an educator with an EdD degree for nine years within the Office of Medical Education at the Children's Hospital National Medical Center, Washington, DC, I feel qualified to list some of the advantages such an individual can bring to a pediatric department:

1. Assist in defining educational goals and objectives;
2. Assist in formulating or improving a curriculum;
3. Consult in research design, educational methodology, and statistics;
4. Collaborate in research projects;
5. Stimulate faculty and trainees to read medical education literature;
6. Assist in developing an evaluation system;
7. Assume responsibility, under physician direction, for coordinating educational programs;
8. Write and secure grants;
9. Help create faculty development programs aimed at faculty, fellows, and residents to improve the quality of education;
10. Assist departments to adopt some of the GPEP principles;
11. Assist in developing underemphasized skills, such as interviewing.

If we as academicians are to prepare physicians for the 21st century by implementing some of the principles in the GPEP report, we have to assure that medical education keeps pace

with technology and information. In the medical model, we seek out consultation from subspecialists when we need reassurance or expert advice about one of our patients. Turning to educational experts to assist us with some of the responsibilities for which we were not trained makes sense and will enable busy academicians to benefit from this association.

LARRIE W. GREENBERG, MD
Office of Medical Education
Children's Hospital
Medical Center
111 Michigan Ave NW
Washington, DC 20010

1. Leuschen MP, Nelson RM Jr, Frias JL: PhDs in pediatric departments. *AJDC* 1988; 142:675-678.
2. Morrow G III: PhD faculty in pediatric departments. *AJDC* 1988;142:598.
3. Fulginiti VA: Another view of PhD faculty in clinical departments. *AJDC* 1988;142:599-600.
4. Greenberg LW, Jewett LS: The GPEP report: A time for change in medical education. *AJDC* 1985;139:1026-1027.
5. Jewett LS, Greenberg LW: Meeting the need for more formalized education in pediatrics. *Med Teach* 1983;5:71-73.

PhD Faculty in the Clinical Department

Sir:—I read with interest the article by Leuschen et al[1] and related commentaries,[2,3] which appeared in the June 1988 issue of *AJDC*, about the role of pediatric research conducted by faculty with doctoral degrees who are not physicians. It seems to me that each of the articles reflected on some of the advantages of research directed by PhD faculty in a clinical department, but considerably more attention was paid to the disadvantages and problems. There is no question, as Dr Fulginiti pointed out, that research conducted by a PhD-trained scientist presents real concerns both for the clinical department and for the individual faculty member. I would submit, however, that as research technologies continue to become more sophisticated and labor-intensive, the necessity for dedicated research faculty becomes essential whether it be by MD- or PhD-trained individuals. The clinician is in a unique position to identify the most important and urgent problems for clinical research efforts, but unfortunately the clinical demands that provide such a global view also restrict the time and effort available to resolve them. The dedicated scientist (MD or PhD) whose major effort is research and whose training is focused on solving scientific problems is best able to pursue major research questions free of the inevitable and necessary time commitment of clinical medicine. All too often the physician dedicated to the practice of medicine finds the university requirement for research a burden while the physician dedicated to research finds the demand of the clinic a burden. Usually one aspect of this dual role suffers. The need for dedicated research faculty in pediatrics is growing more apparent each year as funding becomes more competitive and research projects become more comprehensive. The acceptance of PhD faculty in pediatrics is a real solution to this, and the problems associated with it must be resolved. Implied in this acceptance is the recognition that dedicated clinicians must also have a place in academic medicine free from the requirements of research with equal security.

GLENN J. GORMLEY, MD, PHD
744 Fairacres Ave
Westfield, NJ 07090

1. Leuschen MP, Nelson RM, Frias JL: PhDs in pediatric departments. *AJDC* 1988;142:675-678.
2. Fulginiti VA: Another view of PhD faculty in clinical departments. *AJDC* 1988;142:599-600.
3. Morrow G: PhD faculty in pediatric departments. *AJDC* 1988:142:598.

Discretion Advised When Lowering the Serum Lipid Levels of Children

Sir:—Issues have been raised involving the use of drugs that lower the lipid level and reduce the serum cholesterol level in the general adult population,[1] as well as in infants and children at risk for future development of high serum cholesterol levels.[2] Toward the same goal, dietary modifications have been introduced in the United States that have resulted in increased consumption of polyunsaturated fats (USF) between 1960 and 1975.[3] Linoleic acid intakes from infant formulas have also increased since 1970.[4] This approach to the treatment of hypercholesterolemia may shift a patient's balance toward lipoprotein deficiency, especially during growth and development, and while a great deal is known about the pathologic consequences of hypercholesterolemia, the consequences of hypocholesterolemia are unknown.

We wish to bring the following experimental results to the attention of clinicians interested in reducing serum cholesterol levels. Diets rich in USF[5] and diets containing cholestyramine (CHST)[6] increase the excretion of bile acids, decrease serum lipoprotein levels, and stimulate de novo cholesterogenesis. A decrease in serum low-density lipoprotein (LDL) levels stimulates de novo cholesterogenesis in both the liver and extrahepatic tissues of the rat,[7] and a synchrony between cholesterol and DNA synthesis has been observed.[8,9] The serum LDL level also affects lymphocyte proliferation.[10] A reduction in the serum LDL level seems to act as a mitogenic signal[11] and to underlie the findings of decreased immunity and promotion of chemical tumorigenesis in rats fed diets containing USF[12] and CHST.[13]

Materials and Methods.—We have indeed obtained evidence showing that a drastic reduction in the serum LDL level stimulates not only cholesterogenesis but also DNA synthesis and cell proliferation. Male weanling Wistar rats were fed a control diet or a 4% CHST diet.[13]

Results.—As early as ten days after institution of the diet, CHST-fed animals developed subcutaneous hemorrhages and enlargement of the pancreas, spleen, thymus, and lymph nodes; these animals also showed growth retardation. Serum LDL and very-low-density lipoprotein (VLDL) levels were drastically reduced. An enhancement of cholesterogenesis occurred in the liver, spleen, thymus, kidney, lung, and pancreas; increased DNA synthesis occurred in the spleen and thymus. Histologically, the thymus showed an enlarged medulla with a proliferation of epithelial cells, a reduction of the cortex, and increased numbers of mitoses and of immature lymphocytes. In the spleen, enlargement of the periarterial lymphoid sheaths, increased numbers of mitoses and of immature lymphocytes, and a reduction in the size of B-cell areas were evident. The architecture of the enlarged lymph nodes was completely effaced, with an increase in the number of immature cells. After 60 days of CHST feeding, 94% of the rats were dead.

At the end of ten days of feeding, the control and CHST-fed weanling rats showed the following mean (±SE) relative percentages of serum lipoproteins, respectively: LDL, 37%±2% and 24%±6%; VLDL, 22%±5% and 1%±1%; and high-density lipoproteins, 41%±6% and 74%±6%.

Comment.—The 4% CHST used in these studies is a rather high dose,

and it is difficult to predict whether similar changes can also occur in serum lipoprotein levels in children treated with a low dose of this resin. No studies exist in children,[2] and therefore it is not known whether a reduction in serum LDL and VLDL levels in human infants and children leads to lymphoproliferative disorders, as occurs in weanling rats.

However, our study results[8,11,13] and those of others[10] suggest that lipoproteins not only are important in the absorption and transport of lipids and of fat-soluble vitamins, but that they also act as important signals for growth and cell differentiation. Based on our present knowledge of lipid metabolism, we believe that caution is advised when attempting diet and drug interventions to reduce serum cholesterol levels in healthy children.

MARY E. KAZANECKI
MONA F. MELHEM, MD
K. N. RAO, PHD
Department of Pathology
School of Medicine
University of Pittsburgh
Pittsburgh, PA 15261

1. Consensus Conference: Lowering blood cholesterol to prevent heart disease. *JAMA* 1985; 253:2080-2086.
2. Lloyd JK, West RJ: Childhood prevention of coronary heart disease. *Postgrad Med J* 1986; 62:97-100.
3. Lands WEM: *Fish and Human Health.* New York, Academic Press Inc, 1980.
4. Infant nutrition and cardiovascular disease, editorial. *Lancet* 1988;1:568-569.
5. Ramesha CS, Paul R, Ganguly J: Effects of dietary unsaturated oils on the biosynthesis of cholesterol, and on biliary and fecal excretion of cholesterol and bile acids in rats. *J Nutr* 1980; 110:2149-2158.
6. Myant NB: *The Biology of Cholesterol and Related Steroids.* London, Heineman Medical Books Ltd, 1981.
7. Anderson JM, Dietschy JM: Regulation of sterol synthesis in 15 tissues of rat: II. Role of rat and human high and low density plasma lipoproteins and of rat chylomicron remnants. *J Biol Chem* 1977;252:3652-3659.
8. Rao KN, Kottapally S, Shinozuka H: Acinar cell carcinoma of rat pancreas: Mechanism of deregulation of cholesterol metabolism. *Toxicol Pathol* 1984;12:62-68.
9. Siperstein MD: Role of cholesterogenesis and isoprenoid synthesis in DNA replication and cell growth. *J Lipid Res* 1984;25:1462-1468.
10. Mahley RW: Apolipoprotein E: Cholesterol transport protein with expanding role in cell biology. *Science* 1988;240:622-630.
11. Rao KN: Regulatory aspects of cholesterol metabolism in cells with different degrees of replication. *Toxicol Pathol* 1986;14:430-437.
12. Vitale JJ, Broitman SA: Lipids and immune function. *Cancer Res* 1981;41:3706-3710.
13. Melhem MF, Gabriel HF, Eskander ED, et al: Cholestyramine promotes 7,12-dimethylbenzanthracene induced mammary cancer in Wistar rats. *Br J Cancer* 1987;56:45-48.

Ectrodactyly, Ectodermal Dysplasia, and Clefting Associated With Thymic Aplasia

Sir:—A premature infant was born with ectrodactyly, ectodermal dysplasia, and clefting (EEC) syndrome associated with thymic aplasia, which, to our knowledge, has not been previously reported.

Patient Report.—Our patient, a female infant, was the product of nonconsanguineous parents. The mother had a negative VDRL test result at the 20th week of gestation but a positive (1:128) VDRL test result at the 29th week of gestation. She was treated with penicillin G benzathine (Bicillin) (2.4 million U); she went into premature labor two days later and delivered a 1490-g female infant.

The following abnormalities were noted in the infant: bilateral complete cleft lip and palate with an intermaxillary mass; severely distorted nose and micrognathia; alopecia totalis, with absence of eyebrows and eyelashes; telecanthus with a conjunctival membrane on the right side; and large, floppy, posteriorly rotated ears. The skin showed diffuse vesiculobullous eruptions on the entire body surface, including the palms and soles. The bullae ruptured shortly after birth, leaving large denuded patches of skin, with only occasional islands of preserved intact epidermis. The hands were well formed, with normal crease patterns and normal fingers. The right foot had absent third and fourth toes. The left foot showed fusion of the fourth and fifth toes. Fingernails and toenails were hypoplastic. The initial impression was partially treated congenital syphilis and EEC syndrome. The infant was treated with intravenous crystalline penicillin G and gentamicin. The platelet count was 3.3×10^{12}/L. Gentamicin therapy was discontinued after the onset of acute renal failure. The infant developed severe hypoglycemia and later began to ooze blood from multiple cutaneous sites; ophthalmologic examinations revealed bilateral retinal hemorrhages, and she became hypotensive. Despite appropriate therapy, the infant continued to bleed from the entire skin surface and could not be resuscitated. The infant's VDRL test result was reactive at a 1:8 dilution, and the FTA-ABS test result was strongly positive. The mother at the same time showed a VDRL test result reactive at a 1:64 dilution and her FTA-ABS was also strongly positive. Technical difficulties precluded dark-field examination. Chromosome analysis revealed a normal 46, XX pattern.

Microscopic examination at autopsy revealed that the skin was the site of exuberant *Candida* growth. There was no inflammatory response. Dermal appendages, including the sweat glands, sebaceous glands, and hair follicles, were extremely scarce. The elastic fibers in the dermis, the subcutaneous fat, and the muscles, however, appeared to be normal. There were no spirochetes in any of the tissues examined. In place of the thymus, there was only a small amount of fibroadipose tissue. Microscopic examination of multiple sections taken from this area failed to show any identifiable thymic tissue. This was in contrast to thymic hypoplasia secondary to perinatal stress, which we expected to see.

Comment.—The usual features of EEC syndrome include bilateral cleft lip and/or palate, split feet, hypoplasia of toenails, alopecia totalis, chronic inflammation of the eyes, telecanthus, deformed ears, and poorly formed cutaneous adnexa with inflammation.[1,2]

Ectrodactyly is the most constant feature of EEC syndrome and often affects both feet or hands.[3] In our case, this involvement was confined to the feet. The cases of candidiasis associated with the EEC complex reported in the past have been compatible with the normal survival. Our case is of interest in that the thymic aplasia, with premature birth was widespread candidiasis, curtailed the infant's survival.

MEENAKSHI JHAVERI, MD
SCOTT H. BARNETT, MD
MELVIN GERTNER, MD
YONG-MYUN RHO, MD
JOSEPH C. SEGEN, MD
Mount Sinai School of Medicine
City Hospital at Elmhurst
79-01 Broadway
Elmhurst, NY 11373

1. Bixler D, Spivack J, Bennett J, et al: The ectrodactyly–ectodermal dysplasia clefting (EEC) syndrome. *Clin Genet* 1971;3:43-51.
2. Fried K: Ectrodactyly–ectodermal dysplasia–clefting (EEC) syndrome. *Clin Genet* 1972;3:396-400.
3. Walker JC, Clodius L: The syndrome of cleft-lip, cleft-palate and lobster-claw deformities of hands and feet. *Plast Reconstr Surg* 1963;32:627-636.

98% of subjects tested preferred EryPed*

Kristen thinks EryPed 200

"Tastes like strawberry."

How do you turn defiance into compliance?
Specify the erythromycin kids really like... EryPed.

- Available in delicious mixed-fruit or banana flavor
- Contains no dyes, artificial colors, or preservatives
- Requires no refrigeration
- Offers dosage flexibility—b.i.d., t.i.d., or q.i.d.†
- Can be taken with or without meals

*Data on file, Abbott Laboratories. Flavor evaluations conducted with 20 adult volunteers. Evaluations compared EryPed 200 and 400 to Barre's formulation of erythromycin ethylsuccinate oral suspension, USP 200 mg base/5 ml and 400 mg base/5 ml, respectively.

†q12h, q8h, or q6h.

Write **There's no substitute for compliance**

EryPed® 200, 400 or Drops

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Please see accompanying brief summary of prescribing information.

8113876

THE EXPANDED **EryPed**® LINE, FROM ABBOTT

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Brief Summary of Prescribing Information

DESCRIPTION: Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration.

EryPed 200 and EryPed Drops (erythromycin ethylsuccinate for oral suspension) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 ml (teaspoonful) or 100 mg per 2.5 ml (dropperful) with an appealing fruit flavor. EryPed 400 when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 ml (teaspoonful) with an appealing banana flavor. After mixing, EryPed must be stored below 77°F (25°C) and used within 35 days; refrigeration is not required. These products are intended primarily for pediatric use but can also be used in adults.

Inactive Ingredients EryPed 200, EryPed 400 and EryPed Drops: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum, artificial flavors and other ingredients.

INDICATIONS: *Streptococcus pyogenes* (Group A beta hemolytic streptococcus): Upper and lower respiratory tract, skin, and soft tissue infections of mild to moderate severity.

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

When oral medication is given, the importance of strict adherence by the patient to the prescribed dosage regimen must be stressed. A therapeutic dose should be administered for at least 10 days.

Alpha-hemolytic streptococci (viridans group): Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been suggested by the American Heart Association and American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients hypersensitive to penicillin who have congenital heart disease, or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.[1] Erythromycin is not suitable prior to genitourinary or gastrointestinal tract surgery. NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]

Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

Streptococcus pneumoniae (Diplococcus pneumoniae): Upper respiratory tract infections (e.g., otitis media, pharyngitis) and lower respiratory tract infections (e.g., pneumonia) of mild to moderate degree.

Mycoplasma pneumoniae (Eaton agent, PPLO): For respiratory infections due to this organism.

Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity when used concomitantly with adequate doses of sulfonamides. (See sulfonamide labeling for appropriate prescribing information). The concomitant use of the sulfonamides is necessary since not all strains of *Hemophilus influenzae* are susceptible to erythromycin at the concentrations of the antibiotic achieved with usual therapeutic doses.

Chlamydia trachomatis: For the treatment of urethritis in adult males due to *Chlamydia trachomatis.*

Ureaplasma urealyticum: For the treatment of urethritis in adult males due to *Ureaplasma urealyticum.*

Treponema pallidum: Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae: As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

Corynebacterium minutissimum: For the treatment of erythrasma.

Entamoeba histolytica: In the treatment of intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes: Infections due to this organism.

Bordetella pertussis: Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Legionnaires' Disease: Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

CONTRAINDICATIONS: Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS: Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. There have been reports of hepatic dysfunction, with or without jaundice occurring in patients receiving oral erythromycin products.

Areas of localized infection may require surgical drainage in addition to antibiotic therapy.

Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Usage during pregnancy and lactation: The safety of erythromycin for use during pregnancy has not been established.

Erythromycin crosses the placental barrier. Erythromycin also appears in breast milk.

ADVERSE REACTIONS: The most frequent side effects of erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

HOW SUPPLIED: EryPed 200 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 ml (**NDC** 0074-6302-13), 200 ml (**NDC** 0074-6302-53), and 5 ml unit dose in ABBO-PAC® packages (**NDC** 0074-6302-05). Each 5 ml (teaspoonful) of reconstituted suspension contains activity equivalent to 200 mg erythromycin.

EryPed 400 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 60 ml (**NDC** 0074-6305-60), 100 ml (**NDC** 0074-6305-13), 200 ml (**NDC** 0074-6305-53), and 5 ml unit dose in ABBO-PAC packages (**NDC** 0074-6305-05). Each 5 ml (teaspoonful) of reconstituted suspension contains activity equivalent to 400 mg erythromycin.

EryPed Drops (erythromycin ethylsuccinate for oral suspension) is supplied in 50 ml bottles (**NDC** 0074-6303-50). Each 2.5 ml dropperful (1/2 teaspoonful) of reconstituted suspension contains activity equivalent to 100 mg of erythromycin.

After reconstitution, EryPed must be stored below 77°F (25°C) and used within 35 days; refrigeration not required.

REFERENCE: 1. American Heart Association. 1977. Prevention of bacterial endocarditis. Circulation 56: 139A-143A. 8113876

Abbott Laboratories
North Chicago, IL 60064

INDEX TO ADVERTISERS

Abbott Laboratories 13-14
Allen & Hanburys, Division of Glaxo, Inc. 24A-B, 91

Burroughs Wellcome Company 69-70

Carnation Company 8A-H, 124

East Carolina University 8

Forest Pharmaceuticals, Inc. 8, 71

ICN Pharmaceuticals, Inc. 16-18

Lederle Laboratories 5-6

McNeil Consumer Products Company 19
Mead Johnson Nutritional Division ..... Cover 2

National Biological Corporation 49

Osler Institute 128

Permanente Medical Group 49

Richardson-Vicks, Inc. 92
A.H. Robins Company 23, 72

Sandoz Pharmaceuticals Corporation ..... 2, 15, 47, 97, Cover 3
E.R. Squibb & Sons, Inc. 48-50

University of Alabama 49

Wyeth-Ayerst Laboratories ..... 20, Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

NEW Triaminic® Nite Light™

For 8 full hours of nighttime cough relief for children...

Helps children with coughs and colds get the rest they need...and helps parents rest easier!

Now, a single bedtime dose of new Triaminic NITE LIGHT is all it takes for 8 hours of relief from persistent nighttime cough—often the most troublesome symptom a child suffers.

The maximum pediatric dose of dextromethorphan helps ease nighttime cough while a decongestant and an antihistamine temporarily relieve other cold symptoms that can deprive a child of much-needed sleep.

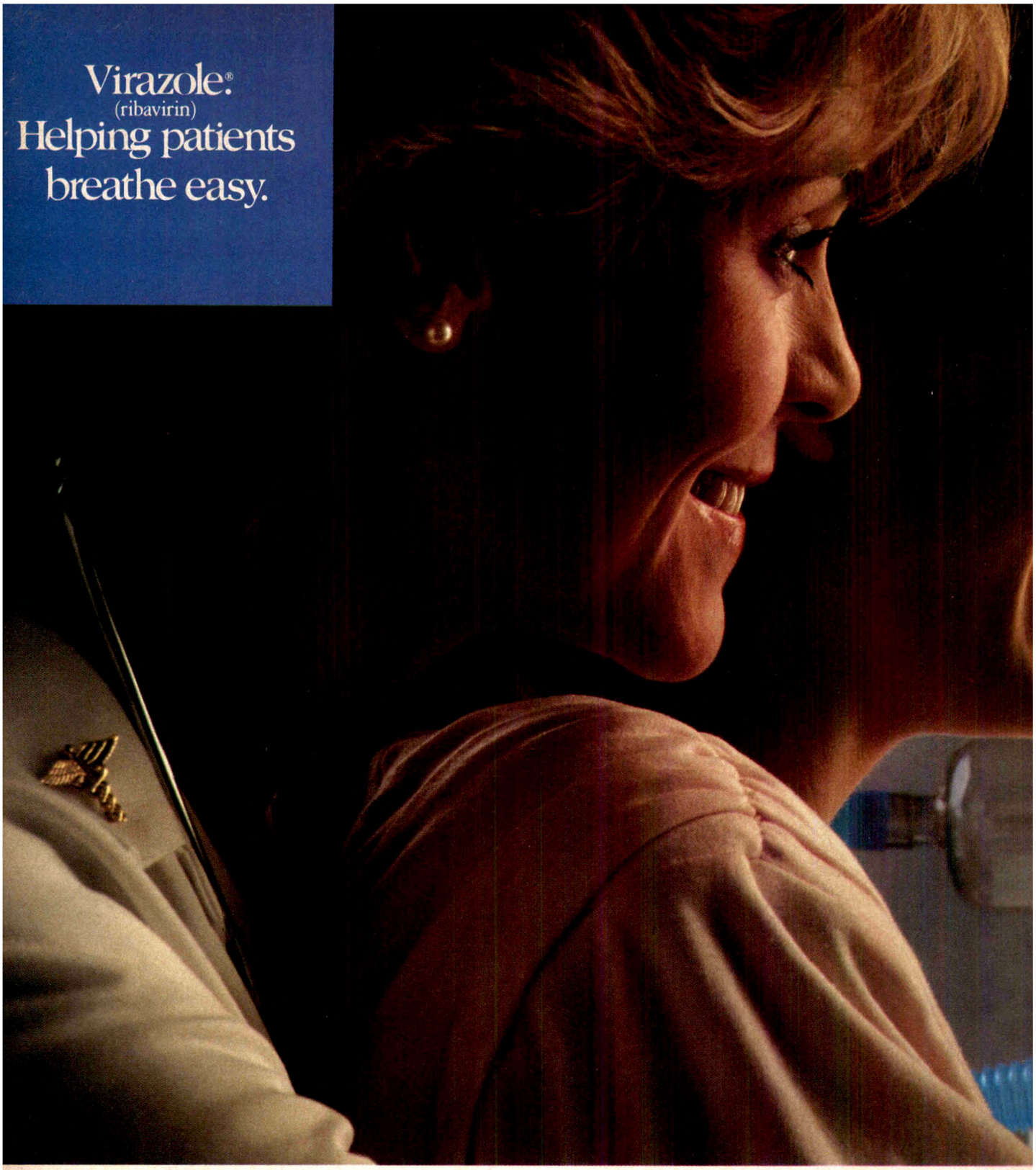
Recommend Triaminic® NITE LIGHT,™ a good night from Triaminic®

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

01882R

© 1989 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

Virazole®
(ribavirin)
Helping patients breathe easy.



Breathe Easy, Virazole on the job.

Virazole® (ribavirin) therapy has been used to treat over 35,000 severely ill infants hospitalized with respiratory syncytial virus (RSV) since its introduction. Ribavirin aerosol has been studied in humans for ten years, and reported side effects have been minimal.[1] Virazole on the job, plus supportive care, means more rapid recovery and easier breathing for babies– and that means "easier breathing" for caregivers and parent

Early diagnosis, early treatment for fast recovery.

Early diagnosis and treatment with Virazole can reduce the severity and duration of RSV infections in infants.[2–4] Ne rapid testing procedures have been developed for RSV that

1. Data on file, ICN Pharmaceuticals, Inc.

2. Hall CB, et al: Ribavirin treatment of respiratory syncytial viral infection in infants with underlying cardiopulmonary disease. *JAMA* 1985;254:3047–3051.

3. Taber LH, et al: Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics* 1983;72:613–618.

4. Hall CB, et al: Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N E J Med* 1983;308:1443–1447.

ke positive diagnosis possible in less than 30 minutes. And
nical evidence and experience continue to confirm that early
tiation of Virazole therapy provides more rapid clinical
provement and may shorten hospitalization.[2-5]

r complete prescribing information, please see next page.

Breathe Easy

Virazole®
(ribavirin)
lyophilized for aerosol administration

cMillan JA, et al: Prediction of the duration of hospi-
tion in patients with respiratory syncytial virus infec-
Use of clinical parameters. *Pediatrics* 1988;81:22–26.

©1988 ICN Pharmaceuticals, Inc. SPI-47

VIRAZOLE® (ribavirin) aerosol is indicated for treatment of severe lower respiratory tract infections due to RSV in carefully selected, hospitalized infants and young children.

Breathe Easy

Virazole®
(ribavirin)

lyophilized for aerosol administration

PRESCRIBING
INFORMATION

WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

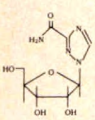
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole®(ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,[1] influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.[2]

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.[3] The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16μg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μM, with a mean concentration of 0.76 μM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 μM, with a mean concentration of 6.8μM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.[3,4] Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.[4]

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence[3,4] or ELISA[5] before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C 3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD_{50} in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION:

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.[3] Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

Virazole®(ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

REFERENCES:

1. Hruska JF, Bernstein JM, Douglas Jr., RG, and Hall CB. Effects of ribavirin on respiratory syncytial virus *in vitro*. *Antimicrob Agents Chemother* 17:770-775, 1 1980.
2. Hruska JF, Morrow PE, Suffin SC, and Douglas Jr., RG. *In vivo* inhibition of respiratory syncytial virus by ribavirin. *Antimicrob Agents Chemother* 21:125-130, 1982.
3. Taber LH, Knight V, Gilbert BE, McClung HW et al. Ribavirin aerosol treatment of bronchiolitis associated with respiratory tract infection in infants. *Pediatrics* 72:613-618, 1983.
4. Hall CB, McBride JT, Walsh EE, Bell DM et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 308:1443-7, 1983.
5. Hendry RM, McIntosh K, Fahnestock ML, and Pierik LT. Enzyme-linked immunosorbent assay for detection of respiratory syncytial virus infection. *J Clin Microbiol* 16:329-33, 1982.

January 1986
R-1-88

ICN Pharmaceuticals, Inc.
ICN PLAZA
3300 HYLAND AVENUE
COSTA MESA, CALIFORNIA 92626
(714) 545-0100

"HOT"

Cool her fever with the brand that offers the most dosage choices

When your patients need fever relief, Children's TYLENOL® acetaminophen should be your first choice. TYLENOL® offers you more dosage choices than any other acetaminophen brand, so your patients get the right medicine in a form and flavor that's right for every child's needs:

- ☐ Alcohol-free Infants' Drops
- ☐ Alcohol-free Children's Elixir in Cherry and *New Grape* flavors
- ☐ Children's 80 mg Chewables in *both* Grape and Fruit flavors
- ☐ Easy-to-swallow 160 mg Junior Strength Coated Caplets for 6- to 14-year-olds

Remember, TYLENOL® is clinically proven as effective an antipyretic as aspirin, with a superior safety profile.[1,2] And parents can easily find your recommendation, because TYLENOL® products are more widely available in food and drug stores than any other brand.[3] So next time a little patient is "Hot!" with fever, make your first choice TYLENOL® acetaminophen.

References: 1. Tarlin L, et al: *Am J Dis Child* 1972;124:880-882. **2.** Aspirin or paracetamol? *Lancet* 1981;II:287-289. **3.** Data on file, McNeil Consumer Products Company.

Children's and Junior Strength

TYLENOL®

acetaminophen

First choice for fever and pain relief

© McN, 1988

McNeil Consumer Products Company
Fort Washington, PA 19034

McNEIL

Bicillin® C-R 900/300

(penicillin G benzathine and penicillin G procaine suspension)

Because compliance doesn't have to depend on who's tending the tots.

WYETH-AYERST LABORATORIES™

Philadelphia, PA 19101

©1987, Wyeth-Ayerst Laboratories

List of 1988 Reviewers for *AJDC*

P 24,241

Few of our readers and authors recognize the enormous contributions that reviewers make to the process of publishing articles in AJDC. *These women and men give unselfishly, and uncompensated, of their time, effort, and consideration to the analysis, judgment, and evaluation of the multitude of manuscripts that are submitted to us each year. This is the only public opportunity that we have to commend and thank them. These reviewers are those active from November 1987 through October 1988.*

Our special appreciation is extended to each person on this list for his or her efforts on behalf of our readers, authors, and editorial staff.—Ed.

Charles Abildgaard
Thomas Aceto, Jr
Raymond Adelman
Phyllis F. Agran
Kyrieckos Aleck
E. Russell Alexander
Charles Alford
Ben L. Allen, Jr
Hugh D. Allen
Bruce Alpert
Arthur J. Ammann
Bascom F. Anthony
Adnano Arguedes
Milton T. Arnold
Balu Athreya
Mary Ellen Avery

Robert Baehner
Michael Bailie
Carol J. Baker
Thomas Balkany
William Banner
Oded Bar-Or
Lewis Barness
Elizabeth Barrett-Connor
James W. Bass
Frederick Battaglia
Robert Beckerman
J. Bruce Beckwith
Alan Bedrick
Marc Beem
Walter Berdon
Larry Beutler
C. Warren Bierman
Anna Binkiewicz
Robert M. Blizzard
Charles E. Bluestone
Richard W. Blumberg
Joel Blumhagen
Thomas F. Boat
Thomas W. Boyce
Timothy Bricker
Helen Britton
John Britton
John G. Brooks
Ben H. Brouhard
Audrey K. Brown
Burnell Brown
George W. Brown
Mark A. Brown
Mark S. Brown
Philip Brunell
Robert Brunner
Allen Buchanan
Rebecca Buckley
Frederick Burg
John Burrington
Sergio Bustamante
L. Joseph Butterfield

Bonnie Camp
Donna Capin
Daniel B. Caplan
Paul Capp
Suzanne B. Cassidy
James D. Cherry
Russell Chesney
Bradley Chipps
Katherine Christoffel
William Cleveland
Stephen Lee Cochi
Melvin L. Cohen
Michael Cohen
George Comerci
Marvin Cornblath
James J. Corrigan, Jr
Susan Coupey
John Crawford
Robert Crone
C. Peter Crowe, Jr
Jan Culbertson
Nancy Cummings

Beverly Dahms
Mary Lou Damiano
Robert Daum
Floyd Denny
Katherine Dewey
Anne E. Dickison
Richard Donnerstein
Allan Drash
Stewart L. Du Ban
Arthur B. Dublin
Patricia K. Duffner
Anne Duggan
Burris Duncan

Kathryn Edwards
Jocelyn Elders
Victor A. Elsberry
Pedro Escobar
Gordon Ewy
John Ey

Fran Farrell
Michael Farrell
Ralph D. Feigin
Murray Feingold
F. Robert Fekety
Timothy Feltes
Gerald W. Fernald
Patricia Ferrieri
Peggy C. Ferry
Laurence Finberg
Richard Fine
Jan Goddard Finegold
Loretta P. Finnegan
Philip Fireman
Delbert Fisher
David Fixler
Alan Fleischman
Norman Fost
Gail Frank
William K. Frankenburg
Douglas Frasier
Patty Freedson
Richard A. Friedman

Lawrence Gartner
Michael Gerber
Victor F. German
Ira Gessner
Lewis E. Gibson
G. Scott Giebink
Paul C. Gillette
Lewis Glasser
Boyd W. Goetzman
Stanley Goldberg
Randall M. Goldblum
Gerald S. Golden
Janet E. Graeber
Dan Granoff
Morris Green
Larrie W. Greenberg
John F. Griffith
Jessie R. Groothuis
Jay Grosfeld
Joyce D. Gryboski
Mary Anne Guggenheim
Margaret F. Guill
Christian Guilleminault
Yezid Gutierrez
Jane V. Gwinn

Caroline Hall
Ronald Hansen
Thomas Hansen
James B. Hanshaw
Virgil Hanson
H. Theodore Harcke
Rita G. Harper
Susan Harris
Gail G. Harrison
William E. Hathaway
Tom Hazinski
Felix Heald
Frederick Hecht
Marilyn Heins
John J. Herbst
Margaret Hilgartner
Alan R. Hinman
Paul John Hletko
Barton Hodes
Joan E. Hodgman
Robert A. Hoekelman
Howard Hoffman
J. Roger Hollister
Douglas S. Holsclaw, Jr
Richard Hong
Virgil Howie
H. Eugene Hoyme
Carl E. Hunt
John J. Hutter
Maureen J. Hutter

David L. Ingram
Kenneth Iserson

Hillel Janai
John D. Johnson
Richard Johnston, Jr
James F. Jones
Nancy R. Joye

Alok Kalia
Michael Kappy
Michael Katz
Robert Katz
Samuel L. Katz
Al Kazniak
James P. Keating
John A. Kirkpatrick, Jr
C. Thomas Kisker
Jerome O. Klein
Paul Kleinman
Hilda Knoblach
Herbert Koffler
Otakar Koldovsky
Beverly Louise Koops
Barbara Korsch
Richard Krugman

Peter Lane
Gary Larsen
Lucien Leape
John LeBrecque

UNIVERSITY OF ILLINOIS LIBRARY

James F. Leckman
Richard Lemen
Harvey Levin
Harold Levine
Melvin Levine
John E. Lewy
Donald Lighter
Elmer S. Lightner
Iris F. Litt
Katherine Lobach
Jennifer Loggie
Timothy Lohman
John Lombardo
Sarah S. Long
Bo Lonnerdal
Gerald Loughlin
Frederick H. Lovejoy, Jr
James Lustig

Donald Ian MacDonald
John Mahan, Jr
Vint Mahesh
M. Jeffrey Maisels
Robert Malina
Melvin I. Marks
Gerald Marx
Robert D. Mauro
Elizabeth R. McAnarnery
Edward McCabe
Paul L. McCarthy
Kenneth McCormick
John P. McGahan
Rima McLeod
Dan G. McNamara
H. Belton Meyer
Richard Michaels
Lyle J. Micheli
Claude Migeon
Denis R. Miller
Beverly C. Morgan
Wayne Morgan
Richard Moriarty
Grant Morrow III
Edward Mortimer
Etsuro Motoyama

Philip Nader
Henry Nadler
Richard Naeye
Marianne Neifert
John D. Nelson
Nicholas Nelson
Eli Newberger
Michael Nihill
Harold Nitowski
Robert Nozza
Elizabeth Nugent

Donough O'Brien
Martin P. O'Laughlin
William Oh
David L. Olds
David Orenstein
Walter Orenstein
James Orlowski
Betty Oseid
Frank Oski
Gary Overturf

Lauren Pachman
Michael Painter
Lu Ann Papile
Jack L. Paradise
Robert Parrott
Robert Pass
Russell Pate
Dennis Patton
David Pearlman
Howard Pearson
Robert Penny
James C. Perry
Georges Peter
Dale Phelps
Roderic Phibbs
Alistair Philip
Barry Pless
Stanley Plotkin
Paul Pollack
Albert W. Pruitt

Paul Quie

Gary Rachelefsky
Michael Radetsky
Isabelle Rapin
C. George Ray
Greg Redding
John Reinhart
John Remington
Gail Richards
Thomas Riemenschneider
Mary Ellen Rimsza
John B. Robbins
Kenneth B. Roberts
William Robertson
Albert Rocchini
Kenneth Rogers
Quentin Rogers
Max Lee Ronis
Allen Root
Jerry Rosenblum
Ron Rosenfeld
Robert Rosenfield
Diana Ross-Trachtman
Alan Roth
Thomas Rowland
Arye Rubinstein
Findlay Russell

David Sahn
Sam Sato
Daniel Savage
James Sayre
Emilie Scarpelli
Barton Schmitt
Irving Schulman
Michael Schumacher
Robert Schwartz
Richard Schwartz
Roland Scott
Elsa Sell
Penelope Shackleford
Daniel C. Shannon
Bennett Shaywitz
Ziad Shehab
Stephen Shelov
Catherine Shisslak
Stanford T. Shulman
William K. Sieber
Frank Sinatra
J. Verne Singleton
Arnold Smith
Ronald Smith
Donald Speer
Mark A. Sperling
Adrian Spitzer
Lewis Sprunger
Sergio Stagno
Carl Stanitski
Barbara Starfield
Mark W. Steele
Alfred Steinschneider
Janet Stewart
E. Richard Stiehm
James Stockman
Sylvan Stool
John Strauss
William B. Strong
Philip Sunshine
John Sutton
Herbert Swick

Nancy Tarbell
Lynn Taussig
David Teele
Anthony Temple
Joel Thompson
Hugh C. Thompson
James K. Todd
Ted Tong
William H. Tooley
Jeffrey Towbin
Doris Trauner
William Truog
David Tubergen

John M. Udall

Yvonne Vaucher
Victor C. Vaughan III
Dan Vernon
Betty Vohr
Joseph Volpe

Jeffrey Wagener
Phillip Walson
Lawrence O. Watkins
William Weil
Barry Weiss
William L. Weston
William Weston III
Richard Whitley
Randall B. Wilkening
Redford Williams
Rickey Williams
Jack H. Wilmore
Beverly P. Wood
Betty Wray
Peter F. Wright

Alayne Yates
Lionel W. Young

Lonnie Zeltzer

In Other AMA Journals

JAMA

Competition, Regulation, and Hospital Costs, 1982 to 1986

J. C. Robinson, H. S. Luft (*JAMA* 1988;260:2676)

Cough and cold therapy as individual as your patients' symptoms.

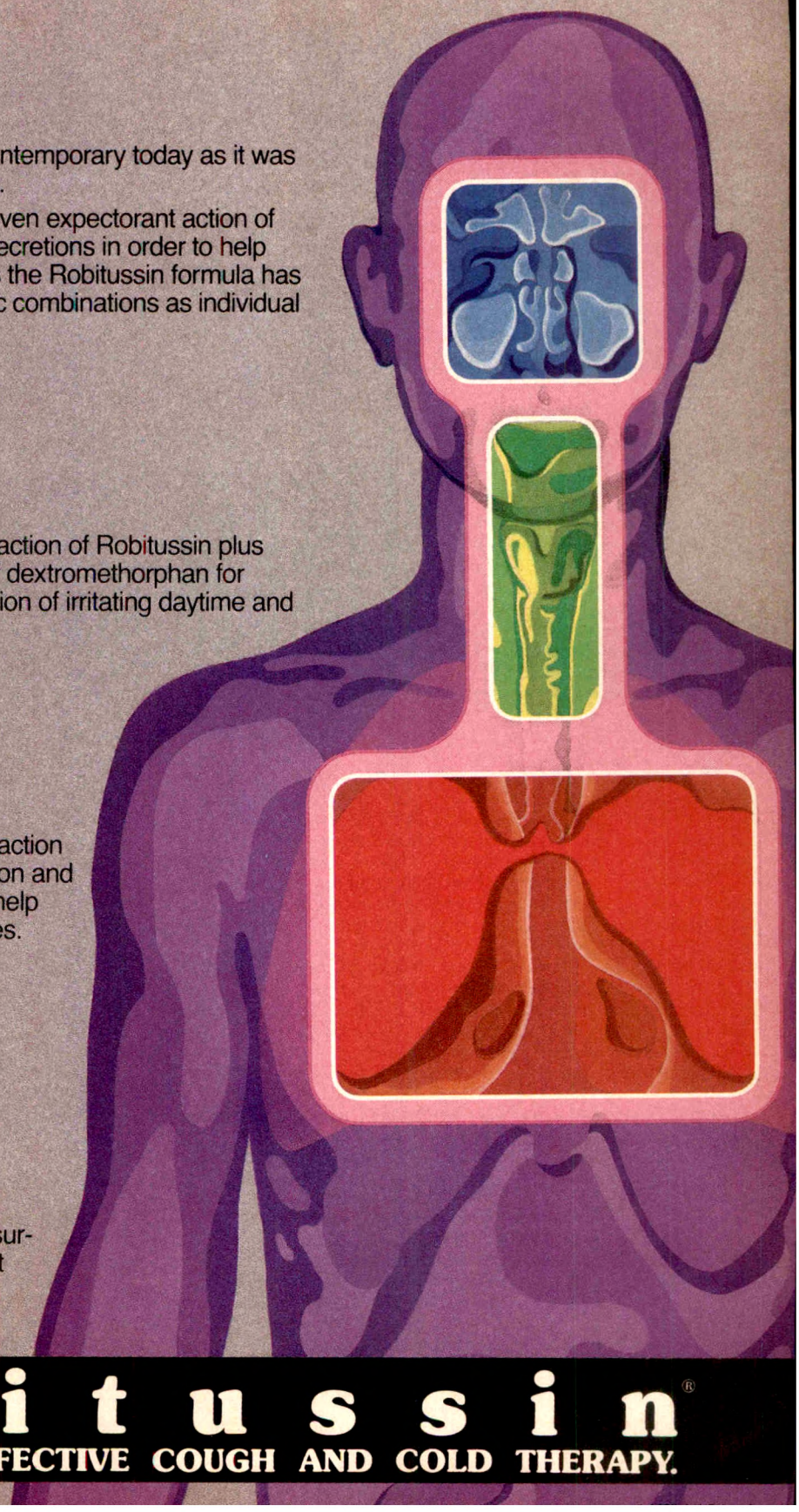
Robitussin® is as contemporary today as it was 40 years ago because efficacy is timeless.

Every Robitussin formula contains the proven expectorant action of guaifenesin to thin and loosen bronchial secretions in order to help clear chest congestion. Through the years the Robitussin formula has been expanded to form special therapeutic combinations as individual as your patients' symptoms.

Robitussin® DM® provides the expectorant action of Robitussin plus the unsurpassed, non-narcotic efficacy of dextromethorphan for effective, centrally acting cough suppression of irritating daytime and nighttime coughs.

Robitussin® PE® provides the expectorant action of Robitussin to help clear chest congestion and adds an effective nasal decongestant to help clear congested nasal and sinus passages.

Robitussin® CF® provides more complete cough and cold relief by combining the expectorant action of Robitussin, the unsurpassed, non-narcotic cough suppressant activity of dextromethorphan and proven nasal congestion relief.



Robitussin®

A TRADITION OF EFFECTIVE COUGH AND COLD THERAPY.

The Editorial Board Speaks . . .

Beverly C. Morgan, MD

"Bev" Morgan has been a faithful member of our Board for nine years. She has been a departmental chairperson at two institutions, the University of Washington, Seattle, and the University of California–Irvine. She resigned the latter post in 1988. Bev has received innumerable honors and has held some of the most important national posts in medicine and pediatrics. Among these are grant review panels of the National Institutes of Health, numerous committees of the American Academy of Pediatrics, and the Graduate Medical Education National Advisory Committee to the Secretary of Health Education and Welfare (the GMENAC panel, which set some standards for physician supply in the United States). Bev has been concerned with the state of pediatric cardiology, with the status of women in medicine and in pediatrics, and with the health care needs of our children. Most recently, together with colleagues at Irvine, she has examined the normal values for blood elements and the prevalence of anemia in children living on selected Pacific atolls.

In this commentary, she provides us with a look at the evolution of pediatric cardiology during her productive tenure in our discipline. It is an excellent summary of the many advances that have occurred in the past several decades.

ADVANCES IN PEDIATRIC CARDIOLOGY

Since my residency, my professional activities have been equally divided between 15 years in pediatric cardiology (teaching research and patient care) and 15 years serving as chairman of two academic pediatric departments. As I now return to full-time cardiology, I have thought much about all of the new diagnostic and therapeutic measures developed in my subspecialty in the past 15 years (and all of the "old," once-infallible techniques, now rarely used, such as dye dilution curves and vector-cardiograms). Even "new" diseases with major cardiac complications have been described (Kawasaki disease), while the pattern of occurrence of "old" diseases seems to be changing (eg, rheumatic fever and the incidence of certain congenital cardiac lesions).

The 1985 Nobel Prize in Medicine or Physiology was awarded to Michael S. Brown, MD, and Joseph Goldstein, MD, for the delineation of familial hypercholesterolemia, one of the most common of all genetic disorders. This represents a milestone in pediatrics and cardiology as well as all of medicine.

Space allows only a brief comment about other major advances and the present summary is neither comprehensive nor detailed. A few selected examples are listed, but no attempt is made to be comprehensive.

Advances in the therapy of congestive heart failure have occurred, and include the development of some skepticism regarding the use of digitalis, particularly in infants with left-to-right shunts. Increasing success with therapy to alter preload and afterload of the heart and the development of new inotropic drugs, together with more effective use of diuretics, have offered alternatives to digitalis for many patients.

Progress in prenatal diagnosis is evolving rapidly. Recently, more traditional testing such as amniocentesis has been supplemented by chorionic villus biopsy, permitting earlier diagnosis. The increasing use of fetal ultrasonography has led to a new field of prenatal cardiac diagnosis by echocardiography and, in some cases, the institution of therapy (conversion of paroxysmal superventricular tachycardia in utero).

For the pediatric cardiologist, the most dramatic change has been the evolution of cardiac ultrasonography, which has proceeded rapidly from the introduction of the M-mode echo (motion mode, a one-dimensional view of the heart) to the addition of cross-sectional or two-dimensional echo (demonstrating spatial, anatomic information). Later, Doppler studies were utilized, supplementing M-mode, two-dimensional echos with physiologic information, allowing the calculation of flow and pressure data as well as providing additional anatomic information. Color Doppler flow is a recent development, and can demonstrate flow and anatomy in multiple colors. This technique is helpful in diagnosing lesions such as valvular stenosis and insufficiency and intracardiac shunts. Color Doppler flow studies have been called "noninvasive angiocardiography." The current state of technology in color Doppler flow is such that some of us familiar with high-quality, biplanar, cine angiocardiograms may not yet find color Doppler to be comparable; the newest Doppler echocardiographic instruments may convert those who are skeptical into believers.

Noninvasive cardiac imaging with an image quality and detail similar to that of the angiocardiogram is presently obtained only by magnetic resonance imaging. While this technique does not require an invasive procedure or injection, it is relatively slow and cumbersome, making its use in the most critically ill pediatric cardiac patients—sick infants—impractical.

The rapid advancement of noninvasive diagnosis has led to a substantial decrease in the number of diagnostic cardiac catheterizations. It has been said that in the future, the majority of cardiac catheterizations in pediatrics may be therapeutic (eg, the catheter blade pulmonary valvotomy).

Finally, mention must be made of cardiac surgery. Infant cardiac transplantation is but one example. This procedure, still considered experimental and performed only in a limited number of cardiac centers, provides palliation for at least a few years for a small number of patients. The surviving infants have, in most cases, normal growth and development and, in infants who otherwise would surely die, a good "quality of life." In addition, refractory life-threatening arrhythmias are now being eliminated by surgery, with excellent results.

I have participated in the evolution of pediatric cardiology for almost 30 years. Great progress has been made since the "early days," when diagnosis by cardiac catheterization and single-plane angiocardiography with "cut film" was the state of the art and open heart surgery was a technique limited to a few lesions in a small number of centers. Today it is truly rewarding to have the opportunity to care for an infant in whom noninvasive imaging has led to cardiac transplantation in the first few days of life, converting a child with a "fatal" lesion (hypoplastic left heart syndrome) into a "normal" infant. What miracles are next?

Passive Freebase Cocaine ('Crack') Inhalation by Infants and Toddlers

David A. Bateman, MD, Margaret C. Heagarty, MD

• Cocaine and its principal metabolite, benzoyl ecgonine, were isolated from the urine of four hospitalized children who had been exposed to the smoke of freebase cocaine ("crack") used by their adult caretakers. Two of the children had transient neurological symptoms (drowsiness and unsteady gait) and two had seizures whose cause could not be determined by laboratory investigation. Passive cocaine inhalation may have caused or contributed to these symptoms. Children in the care of adults who abuse freebase cocaine should be considered at risk not only for disruption of their social environment but also for the effects of cocaine toxicity.

(*AJDC* 1989;143:25-27)

Cocaine abuse among women of childbearing age has increased dramatically in recent years (*New York Times*, Feb 9, 1987, B-1).[1] For example, in 1987 at Harlem Hospital, a municipal institution that serves the indigent black and Hispanic population of central Harlem in New York, the high prevalence of maternal cocaine abuse was indicated by the isolation of cocaine from the urine of over 15% of newborn infants. The cocaine epidemic in New York has been fueled largely by a cheap and available form of freebase cocaine known as "crack," which, when smoked, rapidly attains plasma levels similar to those produced by intravenous cocaine injection.[2-4] The short-lived euphoria from this "crack high" is intensely habituating.

Accepted for publication Sept 27, 1988.

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University (Drs Bateman and Heagarty), New York; and the Newborn Service (Dr Bateman) and Department of Pediatrics (Dr Heagarty), Harlem Hospital, New York.

Reprint requests to Newborn Service, Harlem Hospital, 506 Lenox Ave, New York, NY 10037 (Dr Bateman).

Reports describing the effects of maternal cocaine use on the fetus and infant have referred mainly to those effects produced by alterations of maternal or placental physiology, to the direct transplacental effect of cocaine itself,[1,5-12] or to those effects produced when cocaine is transmitted via breast milk.[13] What happens after birth to infants who continue to be exposed to freebase cocaine used by their caretakers? The present report describes four children, all residents of central Harlem, whose urine contained cocaine, presumably as a result of passive inhalation of crack vapors.

PATIENT REPORTS

PATIENT 1.—A 3½-month-old girl was brought to our hospital emergency ward because of the sudden onset of abnormal movements. These consisted of 30-s episodes of repetitive protruding of the tongue, choking, arching of the back, and brief jerking of both hands, accompanied by a blank stare. The activity stopped without the administration of anticonvulsant medication and the patient was hospitalized for evaluation of a seizure disorder.

The infant had been delivered at term by repeated cesarean section with a birth weight of 3.2 kg and Apgar scores of 8 and 9 at 1 and 5 minutes of age, respectively. The mother had received no prenatal care. The infant had an uneventful course in the nursery and was discharged home with the mother. Her growth and development were normal. She had no history of fever, intercurrent illness, feeding difficulty, or recent immunization. She was fed standard infant formula. Results of a physical examination were normal except for the presence of mild symmetric hyperreflexia and hypertonicity.

Results of laboratory evaluations, including a complete blood cell count, urinalysis, serum levels of electrolytes, calcium, and glucose, and levels of arterial blood gases were normal; lumbar puncture results and an electroencephalogram were normal. Cocaine and its principal metabolite, benzoyl ecgonine, were isolated from the infant's urine by the enzyme-multiplied immunoassay technique (EMIT) and confirmed by radioimmunoassay (RIA).

A history of heavy maternal crack smoking in the presence of the infant was elicited from the maternal aunt and confirmed by the mother. The family was referred to the local child welfare authorities and the infant was discharged to the care of her maternal grandmother two weeks after the admission. Six weeks after admission the child had no further seizure activity and neurologic examination results, growth, and developmental progress were normal.

PATIENT 2.—A 2-year 3-month-old boy was admitted through the emergency ward after a 20-minute seizure was observed by his mother. The seizure occurred at the apartment of the babysitter who cared for the infant while the mother worked. It began during sleep as focal clonic movement in the right lower extremity, became generalized, and subsided after 20 minutes. On admission the child was conscious but lethargic, with normal vital signs and normal results of a neurologic examination. His growth and development appeared to be normal and he showed no signs of infection, malnutrition, or trauma.

The child had been born by normal spontaneous delivery with a birth weight of 3.2 kg. He was discharged home with his mother on the third day of life. He had not been hospitalized or had a major illness until the seizure; he had received no recent immunizations and was not breast-fed. A complete blood cell count, results of a cerebrospinal fluid analysis, and serum levels of electrolytes, calcium, glucose, urea nitrogen, and creatinine were normal. A computed tomographic scan of the head was normal. An electroencephalogram performed five days after admission showed no seizure activity. Blood, urine, and cerebrospinal fluid cultures yielded no organisms. A urine toxicology screen performed by EMIT and confirmed by RIA was positive for cocaine and benzoyl ecgonine.

Within 24 hours of hospitalization the patient was alert and active and remained so for the four days of hospitalization. Results of a neurologic examination were normal and the patient had no more seizures.

The patient's mother denied using cocaine or other illicit drugs. She said that crack was sold in the building where the babysitter lived and she accused the babysitter of smoking the drug in the child's presence. A careful home evaluation by the hospital social service department apparently confirmed the mother's allegations and the child was returned to her care. At a follow-up examination one month later, the infant had experienced no further seizures and results of the neurologic examination remained normal.

PATIENT 3.—A 9-month-old boy was admitted for treatment of partial-thickness burns of the neck, back, and right forearm that, according to his mother, he received when he fell out of bed and lodged against a hot steam radiator. The burns covered approximately 5% of his body. Despite the painful nature of the burns the child seemed unusually drowsy. A toxicological study of the urine by EMIT and RIA methods was positive for both cocaine and opiates.

The infant's medical history was normal, with no intercurrent illnesses reported by the mother. His growth and development were normal for his age. He had not been breast-fed but had received only standard commercial baby food and formula.

The child's drowsiness resolved quickly and the burns had healed by epithelialization two weeks after admission. He showed no seizure activity or neurologic abnormalities. The mother gave a history of occasional alcohol and marijuana use but denied the use of opiates, cocaine, or crack. She said that both her brothers were heavy abusers of freebase cocaine and other drugs, and that during a 12-hour period before the child's admission the brothers had smoked drugs heavily in the poorly ventilated apartment in a room adjacent to where the infant slept. Because of the apparent drug intoxication of the infant and the suspicious nature of the burn, the family was referred to Special Services for Children, who, after an investigation of the home, obtained a court order banning the brothers from the apartment. The infant was discharged to the care of the mother three weeks after the incident occurred. He was unavailable for follow-up.

PATIENT 4.—A 3-year 11-month-old boy was brought to the emergency ward by his mother, who claimed that he had awakened in the morning complaining of nausea and was too "wobbly" to stand up. These symptoms persisted despite an offer of breakfast at his favorite fast-food restaurant.

He was evaluated several hours later in our emergency ward. Results of his physical and neurologic examinations, complete blood cell count, and serum levels of electrolytes, calcium, glucose, urea nitrogen, and creatinine were normal. Urine obtained for toxicological screening by EMIT and RIA methods contained cocaine. He was admitted to the pediatric ward and the family was referred to Special Services for Children for investigation.

The child lived with his mother and her female roommate in a three-room apartment with poor ventilation. The mother related that during the night before the child's admission she had left him with her roommate. She returned in the morning to find the apartment filled with smoke from freebase cocaine apparently smoked by her roommate's boyfriend. The child confirmed that the adults had been "smoking all night." After a lengthy investigation by Special Services for Children, the child was returned to the care of his mother.

COMMENT

These four children whose urine contained cocaine appear to have been passively exposed to the smoke of freebase cocaine used by their adult caretakers. Unlike tobacco smoke, for which the hazards of environmental pollution have been well documented,[14] there appear to be no reports of the effects of passive freebase cocaine inhalation in humans or in laboratory animals. The fetal and neonatal effects of cocaine abuse by pregnant women are currently under intensive investigation. Increased rates of intrauterine growth retardation,[8,9] abruptio placenta,[5-9] stillbirth,[8] congenital anomalies,[8] and abnormal respiratory patterns[10] have been reported in the newborn infant in association with maternal cocaine abuse. Neurologic complications in the newborn infant exposed to cocaine in utero include abnormal interactive behavior and state organization as measured by the Brazelton examination,[7] irritability, tremulousness, hypertonicity,[9,12] and cerebral infarctions.[12] Chasnoff et al[13] reported irritability and tremulousness in a 2-week-old infant nursed by a cocaine-abusing mother; cocaine and benzoyl ecgonine were isolated both from the infant's urine and the mother's milk.

Neonatal seizures related to transplacental cocaine exposure have not been recognized; however, Chaney et al[15] described convulsions in an 11-day-old breast-fed infant whose mother used topical cocaine powder to relieve nipple soreness. In adults, acute cocaine toxicity may result in seizures, either through the direct effect of cocaine[16] or from other complications of cocaine toxicity, including intracranial hemorrhage, severe hypertension, hyperthermia, cardiac arrhythmias, and myocardial infarction.[6,17-19]

Evidence linking the passive inhalation of freebase cocaine to any of the presenting symptoms of illness in the patients described in the present report is circumstantial but provocative. We have noted that none of the children was being breast-fed at the time the symptoms occurred, nor were there indications that any child had been given cocaine directly or had ingested the drug himself or herself. The seizures described in patients 1 and 2 were brief, appeared to have occurred following intense cocaine exposure, and resolved without sustained anticonvulsant treatment. Neither child displayed any obvious features of infectious, metabolic, or inherited cause of the seizures; neither child had experienced previous convulsions, received recent immunizations, or had fever. The seizures did not recur and both children were apparently normal at follow-up examinations.

Patients 3 and 4 each experienced an episode of intense freebase cocaine exposure followed by transient neurologic symptoms (drowsiness/unsteadiness of gait). Whether or not these symptoms were due to passive freebase cocaine inhalation cannot be determined with certainty, particularly in the case of patient 3, from whose urine opiates as well as cocaine were isolated. These cases emphasize the difficulties faced by physicians and other care givers in assessing the causes of illness of children in the care of adults who use cocaine and other drugs. Obviously these children are at high risk for abuse or neglect by a variety of means, and the historical data needed to ascertain that risk are rarely straightforward.

In summary, four children who had been heavily exposed to the smoke of freebase cocaine required medical attention for transient neurologic symptoms, including seizures. Clinicians, particularly those working in areas where crack abuse is epidemic, should be alert to the possible causative role of freebase cocaine in intoxicated infants and children. However, the role of cocaine in such cases as these will become clear only when the environmental hazards posed by aerosolized cocaine are studied experimentally.

References

1. Gawin FH, Ellinwood EH: Cocaine and other stimulants: Action, abuse and treatment. *N Engl J Med* 1988;318:1173-1182.
2. Jekel FJ, Allen DF, Podlewski H, et al: Epidemic freebase cocaine abuse. *Lancet* 1986;1: 459-462.
3. Siegel RK: Cocaine smoking. *N Engl J Med* 1979;300:373.
4. Van Dyke C, Byck R: Cocaine. *Sci Am*, March 1982, pp 128-141.
5. Acker D, Sachs BP, Tracey KJ, et al: Abruptio placenta associated with cocaine use. *Am J Obstet Gynecol* 1983;146:220-221.
6. Cregler LL, Mark H: Medical complications of cocaine abuse. *N Engl J Med* 1986;315:1495-1499.
7. Chasnoff I, Burns WJ, Schnoll SH, et al: Cocaine use in pregnancy. *N Engl J Med* 1985;313: 666-669.
8. Bingol N, Fuchs M, Diaz V, et al: Teratogenicity of cocaine in humans. *J Pediatr* 1987;110:93-96.
9. Livesay S, Ehrlich S, Finnegan LP: Cocaine and pregnancy: Maternal and infant outcome, abstracted. *Pediatr Res* 1987;21:238A.
10. Riley JG, Porat R: Abnormal pneumograms in infants with in utero cocaine exposure, abstracted. *Pediatr Res* 1987;21:262A.
11. Cherukuri R, Minkoff H, Parekh A, et al: Alkaloidal cocaine ('crack') in pregnancy: A prospective study, abstracted. *Pediatr Res* 1987;21:233A.
12. Chasnoff I, Bussey ME, Savich R, et al: Perinatal cerebral infarction and maternal cocaine use. *J Pediatr* 1986;108:456-459.
13. Chasnoff IJ, Douglas EL, Squires L: Cocaine intoxication in a breast-fed infant. *Pediatrics* 1987;80:836-838.
14. *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General.* Rockville, Md, US Dept of Health and Human Services, Office on Smoking and Health, 1986.
15. Chaney NE, Franke J, Wadlington WB: Cocaine convulsions in a breast-feeding baby. *J Pediatr* 1988;112:134-135.
16. Post RM, Kopanda RT, Black KE: Progressive effects of cocaine on behavior and central amine metabolism in rhesus monkeys: Relationship to kindling and psychosis. *Biol Psychiatry* 1976;11:403-419.
17. Ritchie JM, Greene NM: Local anesthetics, in Goodman LS, Gilman AG, Roll TW, et al (eds): *The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co Inc, 1985, pp 309-310.
18. Jonsson S, O'Meara M, Young JB: Acute cocaine poisoning. *Am J Med* 1983;75:1061-1064.
19. Myers JA, Earnest MP: Generalized seizures and cocaine abuse. *Neurology* 1984;34: 675-676.

Book Review

Diagnostic Imaging in Paediatrics, edited by Isky Gordon, London, Chapman & Hall Ltd (distributed by Sheridan House Inc, Dobbs Ferry, NY), 313 pp, with illus, $79.50, 1987.

This is a well-illustrated, 313-page book aimed specifically at pediatricians or family practitioners. It introduces modern concepts of diagnostic imaging, limitations of these techniques, and pathophysiologic correlates.

The book is organized into an introductory section in which methods and techniques of imaging, dosimetry, and contrast material are discussed. There is then a short chapter on psychology, followed by sections related to organ systems or specific disease entities (abdominal mass, oncology and hematology, and hypertension).

There are a number of flow diagrams used throughout the book. These are useful, but it is important for the clinician to bear in mind that the radiologist is the best source for discussion of the next step in imaging, and that each radiologist may differ in his or her approach to imaging.

A number of useful tables are included, giving a rapid overview of the possible differential diagnoses to be considered. There are a large number of figures, usually with detail given in the caption. In general the figures are of good quality, although those that represent chest roentgenograms are the poorest (with computed tomographic scans representing the best overall quality). The figures do illustrate the abnormalities; however, the more frequent use in some sections of labels and arrows to indicate abnormalities or identify anatomic structures would have better aided the nonradiologist readers.

The book is up to date in its discussion of contrast material and the many different imaging modalities, including nuclear medicine, computed tomography, and magnetic resonance imaging. Pertinent and timely references are included.

Overall, *Diagnostic Imaging in Paediatrics* will assist the clinician seeking an introduction to diagnostic imaging. The volume is short and concise. It is somewhat superficial, but generally accurate and current. Pediatricians, general practitioners, and beginning diagnostic radiology residents will find it useful.

Beverly P. Wood, MD
University of Rochester Medical Center
601 Elmwood Ave
PO Box 648
Rochester, NY 14642

Haemophilus B Polysaccharide Vaccine

Antibody Kinetics in 17- to 71-Month-Old Children

CPT Keith P. Ramsey, MC, USA; COL Lou A. Popejoy, MC, USA;
CPT Steven W. Jesse, MC, USA; CPT Ines Gonzales-Torres, MC, USA

• The antibody response to polysaccharide vaccines is well known to be age variable, with younger infants or children responding less dependably and with lower antibody levels. The fate of these induced antibodies over time is less well understood. We studied the antibody kinetics of β-Capsa 1, a *Haemophilus B* polysaccharide vaccine, in 185 children aged 17 to 71 months. Ninety percent of the children vaccinated at age 2 years or older achieved reportedly immune serum antibody levels three weeks after vaccination; 45% vaccinated at age 18 months achieved such levels. In six months, the antibody levels fell significantly in all children. In those vaccinated at age 18 months, the levels six months after vaccination were not significantly different from those prior to vaccination. Our study raises the possibility that antibody kinetics may be as critical a consideration as immediate antibody response in deciding the proper clinical use of a polysaccharide-based vaccine.

(*AJDC* 1989;143:28-30)

In 1974, a field trial was conducted in Finland in which a polysaccharide vaccine against *Haemophilus influenzae* type B (HiB) was administered.[1-3] It was shown to be both safe and effective in producing antibodies against the HiB capsular polysaccharide polyribosylribitol phosphate (PRP), which had previously been shown capable of preventing invasive HiB disease.[1-6] Based on the reported protective efficacy of 90% in that study, a similarly prepared vaccine, *Haemophilus* B polysaccharide vaccine (HBPV), was licensed in the United States in 1985.

See also p 31.

The Finnish study also showed, however, that their vaccine, like all polysaccharide vaccines, induced poor antibody response and duration in younger infants and children.[1,3,7,8] This was the reason that, although the greatest period of risk for invasive HiB disease was and remains less than age 18 months, HBPV was not recommended for routine use for children under age 2 years.[9-11] Although the vaccine was approved for high-risk groups at age 18 months, the recommendations were unclear as to the need or timing of revaccination.[9,10,12,13]

The initial purpose of our study was to clarify the need or timing for revaccination with HBPV by documenting the immunokinetics of HBPV in children at different ages. We studied the immediate antibody response and duration at six to eight months following vaccination in 17- to 71-month-old infants and children in our test population.

PATIENTS AND METHODS

The study was conducted at William Beaumont Army Medical Center in El Paso, Tex. Informed consent was obtained from the parents of 185 children aged 17 to 71 months for participation in the study. The racial-ethnic composition of our study group was 60% Caucasian, 20% Hispanic (by Spanish surname), and 4% Asian. One hundred fifteen children, aged 2 to 5 years, were vaccinated in the fall of 1985; 70 children, aged 17 to 19 months, were vaccinated between the spring and fall of 1986. All were vaccinated intramuscularly with a dose of the HiB polysaccharide vaccine β-Capsa 1, containing 25 μg of polysaccharide antigen.

Serum samples were obtained before immunization (n = 185), three weeks after immunization (n = 183), and six to eight months after immunization (n = 112). Serum antibody levels of the HiB capsular polysaccharide PRP were determined by Praxis Biologics Inc (Rochester, NY) by Farr radioactive antigen-binding assay using the new Rochester tritiated PRP antigen.[14] Results were standardized to the Office of Biologics Research and Review of the US Food and Drug Administration standard of 70 mg/L.[15]

Study participants were classified into five age divisions based on age at vaccination: 17 to 19 months old (n = 70); 24 to 35 months old (n = 35); 36 to 47 months old (n = 30); 48 to 59 months old (n = 36); and 60 to 71 months old (n = 14). Serum antibody levels were grouped by both time of collection and the age of the participant. Geometric mean antibody levels were calculated for each group and are presented in the Table and the Figure . For each age division, a one-factor analysis of variance and Scheffé's test were performed on the repeated measures of the serum sample antibody levels over the six- to eight-month span of the study. All missing values were converted to the calculated geometric mean values specific for each age group and serum sample group.

RESULTS

The Table presents the specific geometric mean anti-PRP levels of the different age divisions for each serum sample collection. There was a significant ($P \leq .05$) rise in the anti-PRP levels from before to three weeks after vaccination in all age groups. There was a significant decline in all age groups between three weeks and six to eight months after vaccination.

The Figure demonstrates how the initial antibody response to vaccination increased with the age of the vaccinee. It also shows the fall in antibody level over the six- to eight-month postvaccination period. Compared with the immediate antibody response, the later antibody levels were only 42% in the 24- to 35-month-olds, 51% in the 36- to 47-month-olds, 37% in the 48- to 59-month-olds, and 70% in the 60- to 71-month-olds. In the infants vaccinated at age 17 to 19

Accepted for publication July 25, 1988.

From the Department of Pediatrics, William Beaumont Army Medical Center, El Paso, Tex.

This study was a finalist for the Howard Johnson Award, Uniformed Services Pediatric Seminar, San Diego, March 1988.

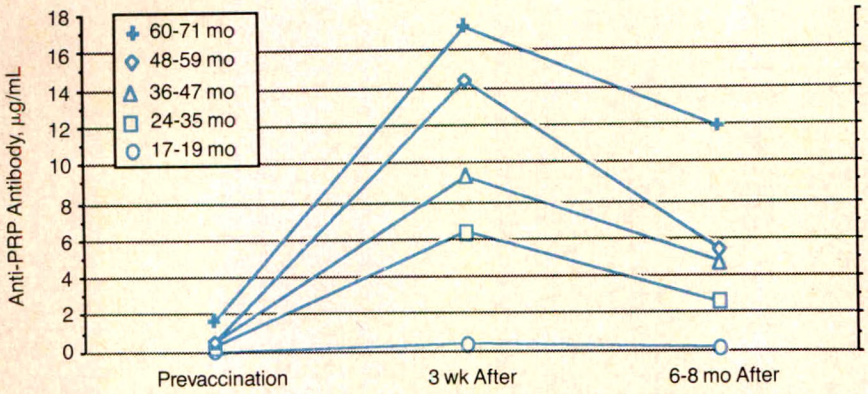
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or Department of Defense.

Reprint requests to Department of Pediatrics, William Beaumont Army Medical Center, El Paso, TX 79920-5001 (Dr Popejoy).

Geometric Mean Anti–Polyribosylribitol Phosphate (PRP) Antibody Levels Before, Three Weeks After, and Six to Eight Months After Vaccination

Age, y	Anti-PRP Level, mg/L		
	Before	3 wk After	6 to 8 mo After
1.5	0.17 (n=70)	0.53 (n=69)	0.27 (n=25)*
2	0.36 (n=35)	6.46 (n=35)	2.77 (n=26)
3	0.64 (n=30)	9.47 (n=29)	4.83 (n=21)
4	0.62 (n=36)	14.49 (n=36)	5.40 (n=29)
5	1.70 (n=14)	17.43 (n=14)	12.06 (n=11)

*There is no significant difference between this value and that before vaccination.



Geometric mean anti–polyribosylribitol phosphate (PRP) antibody levels in children aged 17 to 71 months or older.

months, the antibody level fell to a value not significantly different from that before vaccination.

COMMENT

Our results document three observations about anti-PRP polysaccharide antibodies in a multiethnic population of children in the United States. First, the prevaccination antibody levels document the pattern of the "natural" acquisition of these antibodies. Second, the three-week postvaccination levels document the immunogenicity of HBPV in inducing these antibodies. Third, the antibody levels determined on the last serum samples drawn complete the immunokinetic data for the first six to eight months after vaccination.

Natural Antibody Acquisition

Studies have demonstrated that the pattern of the natural acquisition of anti-PRP antibodies varies among countries and among racial/ethnic groups within the United States.[4-5,16,17] These differences in patterns have been associated with shifts in the age-specific incidence of systemic HiB disease.[16-22]

The pattern in our population of increasing prevaccination antibody levels with age was similar to that described in the Scandinavian countries, where a shift in HiB disease toward older children has been noted.[22] Using the prevaccination anti-PRP antibody level of 0.15 mg/L, which the Finnish study found clinically correlated with immunity,[23-24] 24% of our 18-month-olds, 49% of our 2-year-olds, 60% of our 3-year-olds, 72% of our 4-year-olds, and 86% of our 5-year-olds had naturally acquired immunity. There were no significant diffrences in the levels among the racial/ethnic groups in our study, implying that the previously reported differences among these groups were mainly socioeconomic rather than genetic in origin.

Antibody Response to Vaccine

The antibody response to PRP has been shown to be age sensitive, with infants responding infrequently and with less antibody than do older children or adults.[4,5] The percentage of responding individuals has been reported to increase significantly during the second year of life.[3,5,25,26] In addition, racially and genetically related variation in antibody response has been noted.[26] Using a three-week postvaccination level of 1.0 mg/L as an adequate response, the Finnish experience was that approximately 50% responded at age 16 to 18 months, increasing to 90% at age 2 years.[3,24]

Our population showed a response virtually identical to that of the Finnish study, with 45% responding at age 17 to 19 months and 91% responding in their second year of life. There was no significant difference in the antibody response of our racial/ethnic groups.

Antibody Decrease Following Vaccination

Anti-PRP antibody levels maintained beyond the immediate postvaccination period were not similar between our population and the Finnish population. Our results demonstrated a more rapid and age-sensitive decline in antibody levels.

Most studies have evaluated only the initial response to HBPV by limiting their serum sample collections to three or four weeks after vaccination. The Finnish data are the standard for anti-PRP immunokinetics reporting antibody levels drawn at various times up to 3½ years after vaccination, which were correlated with the occurrence of HiB disease.[8] Specifically, infants vaccinated at younger than age 18 months were first remeasured in six months; children older than age 18 months were first remeasured in 18 months. The important difference in our study other than the composition of our population is that we designed it to remeasure the older children sooner and to divide the 18- to 35-month-olds into two age groups.

Both our study and the Finnish study demonstrated a significant decline in postvaccination antibody levels in all age groups.[8] The decline in both populations was, like initial response, variable by age. In children vaccinated at age 3 years or older, the degree of antibody decline seen in the Finnish population at 18 months after vaccination was seen in our population by six to eight months.

More significant were the results in those children under age 3 years. The Finnish study noted that infants vacci-

nated at age 3 to 17 months had antibody levels fall within six months to levels no different than unvaccinated infants at the same age.[1] We saw the same result in our infants aged 17 to 19 months. Disturbingly, this immunokinetic pattern was associated with lack of clinical protection in the Finnish study.

Owing to different age groupings, it is more difficult to directly compare the US and Finnish children vaccinated between ages 1½ and 3 years. The Finnish children vaccinated in this age range had antibody levels decline by approximately half at 18 months after vaccination. We saw a fall in the antibody levels in our population of almost 60% within only six to eight months. It is noteworthy that the only two cases of bacteremic HiB disease in the Finnish study occurred at 19 and 21 months after vaccination in children vaccinated at 17 and 24 months, respectively.[8]

It is possible that differences in the antibody kinetics between our population and the Finnish population are artificial. Edwards et al[15] raised significant concerns about the lack of comparability between assay antigens, particularly the new Rochester antigen, which was used in the assay of our population's serum samples. Our focus on comparing relative declines rather than absolute values was an attempt to respond to the issues they raised. Furthermore, their observations lead one to expect higher values before and after vaccination in our study compared with the Finnish study, which was not the case. Their observations also lead one to expect that postvaccination antibody level declines would be understated in our population rather than overstated. Although the comparability issue in our study cannot be fully resolved, we do feel the data support the conclusion that the differences between our study and the Finnish study are not artificial.

It is possible that differences in the antibody kinetics between our population and the Finnish population, if not artificial, are only apparent. This would be the case if almost all the antibody decrease in the Finnish study occurred within the first six months, remembering that they did not draw serum samples until 18 months after vaccination. Since the antibodies in the Finnish population continued to decrease over the next two years,[8] it seems more likely that the antibody response in our population was not just apparent, but actually less sustained and more age sensitive. Whether the rapid fall was true of both populations or just ours, antibody levels were found within six to eight months to be much lower than had been expected based on the original Finnish data. Our study raises the question whether immunokinetics may have played a role, if not the major role, in explaining the less-than-expected immunogenicity of HBPV reported in the United States.[27]

SUMMARY

Polysaccharide vaccines are known to induce less intense and durable antibody responses in infants and young children. Our study documented this to be true of a licensed HiB capsular polysaccharide vaccine to a greater degree than expected. The clinical implication is that antibody kinetics may play a greater role in this vaccine efficacy than previously appreciated.

The introduction of the newer conjugated HiB vaccines was based on the expectation that the protein conjugation would lead to more and longer-lasting antibodies at younger ages.[28] Our study supports considering antibody kinetics in the evaluation of the new vaccines and in recommendations for their use in revaccination.

References

1. Peltola H, Käyhty H, Sivonen A, et al: *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: A double-blind field study of 100 000 vaccinees 3 months to 5 years of age in Finland. *Pediatrics* 1977;60:730-737.

2. Mäkelä PH, Peltola H, Käyhty H, et al: Polysaccharide vaccines of group A *Neisseria meningitidis* and *Haemophilus influenzae* type b: A field trial in Finland. *J Infect Dis* 1977;136(suppl): S43-S50.

3. Peltola H, Käyhty H, Virtanen M, et al: Prevention of *Haemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. *N Engl J Med* 1984;310:1561-1566.

4. Robbins JB, Parke JC, Schneerson R, et al: Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. *Pediatr Res* 1973;7:103-110.

5. Smith DH, Peter G, Ingram DL, et al: Responses of children immunized with the capsular polysaccharide of *Haemophilus influenzae* type b. *Pediatrics* 1973;52:637-644.

6. Peter G, Smith DH: *Hemophilus influenzae* meningitis at the Children's Hospital Medical Center in Boston, 1958 to 1973. *Pediatrics* 1973;55: 523-526.

7. Granoff DM, Cater KL: *Haemophilus influenzae* type b polysaccharide vaccines. *J Pediatr* 1985;107:330-336.

8. Käyhty H, Karanko V, Peltola H, et al: Serum antibodies after vaccination with *Haemophilus influenzae* type b capsular polysaccharide and responses to reimmunization: No evidence of immunologic tolerance or memory. *Pediatrics* 1984; 74:857-864.

9. Centers for Disease Control, Immunization Practices Advisory Committee: Polysaccharide vaccine for prevention of *Haemophilus influenzae* type b disease. *MMWR* 1985;34:201-205.

10. Committee on Infectious Diseases, American Academy of Pediatrics: *Haemophilus influenzae* infections, in Peter G (ed): *Report of the Committee on Infectious Diseases*, ed 20. Elk Grove Village, Ill, American Academy of Pediatrics, 1986, pp 173-174.

11. Cochi SL, Broome CV, Hightower AW: Immunization of US children with *Haemophilus influenzae* type b polysaccharide vaccine: A cost-effectiveness model of strategy assessment. *JAMA* 1985;253:521-529.

12. Cochi SL, Fleming DW, Hull HF, et al: *Haemophilus influenzae* b polysaccharide vaccine: Physician acceptance and use of a new vaccine. *AJDC* 1986;140:1226-1230.

13. Cochi SL, Broome CV: Vaccine prevention of *Haemophilus influenzae* type b disease: Past, present and future. *Pediatr Infect Dis J* 1986; 5:12-19.

14. Anderson P: Intrinsic tritium labeling of the capsular polysaccharide antigen of *Haemophilus* type B. *J Immunol* 1978;120:866-870.

15. Edwards K, Decker P, Porch C, et al: Lack of comparability between commonly used serological assays of immune response to *Haemophilus influenzae* vaccine. *J Infect Dis* 1987;155:283-291.

16. Anderson P, Smith DH, Ingram DL, et al: Antibody to polyribophosphate of *Haemophilus influenzae* type b in infants and children: Effect of immunization with polyribophosphate. *J Infect Dis* 1977;136:S57-S62.

17. Haroche G, Lang T, Rea D: *Haemophilus influenzae* type b vaccine. *N Engl J Med* 1985;312:53-54.

18. Ward JL, Lum MK, Margolis HS, et al: *Haemophilus influenzae* disease in Alaskan Eskimos: Characteristics of a population with an unusual incidence of invasive disease. *Lancet* 1982;1:1281-1285.

19. Coulehan JL, Michaels RH, Williams KE, et al: Bacterial meningitis in Navajo Indians. *Public Health Rep* 1976;91:464-468.

20. Coulehan JL, Michaels RH, Hallowell C, et al: Epidemiology of *Haemophilus influenzae* type b disease among Navajo Indians. *Public Health Rep* 1984;99:404-409.

21. Losonsky GA, Santosham M, Sehgal VM, et al: *Haemophilus influenzae* in the White Mountain Apaches: Molecular epidemiology of a high risk population. *Pediatr Infect Dis J* 1984;3:539-547.

22. Claesson B, Trollfors B, Jodal U, et al: Incidence and prognosis of *Haemophilus influenzae* meningitis in children in a Swedish region. *Pediatr Infect Dis J* 1984;3:35-39.

23. Käyhty H, Peltola H, Karanko V, et al: The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1983;147:1100.

24. Anderson P: The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1984;149:1034.

25. Pincus DJ, Morrison D, Andrews C, et al: Age related response to two *Haemophilus influenzae* type b vaccine. *J Pediatr* 1982;100:197-201.

26. Granoff DM, Munson RS Jr: Prospects for prevention of *Haemophilus influenzae* type b disease by immunization. *J Infect Dis* 1986;153: 448-461.

27. Daum R: Perspectives on the current *Haemophilus* vaccine. *Pediatr Infect Dis J* 1987;6:6-7.

28. Centers for Disease Control: ACIP update: Prevention of *Haemophilus influenzae* type b disease. *MMWR* 1988;37:13-16.

Immunization After Invasive *Haemophilus influenzae* Type b Disease

Serologic Response to a Conjugate Vaccine

Kathryn M. Edwards, MD; Michael D. Decker, MD, MPH;
Carol R. Porch, MD; Pamela Palmer, MS; Roberta Bradley, MSN

• Fifteen children with previous invasive *Haemophilus influenzae* type b disease were immunized with a *Haemophilus*-diphtheria toxin mutant protein conjugate vaccine. Serologic responses were compared with those of 31 newly immunized children without previous invasive *H influenzae* type b disease. Mean levels of antibody to polyribosylribitol phosphate among study children younger than 18 months were 0.086 mg/L before immunization, 0.737 mg/L after first immunization, and 4.453 mg/L after second immunization. In contrast, the comparable mean polyribosylribitol phosphate antibody levels among control children younger than 18 months were 0.107, 3.580, and 63.502 mg/L. A similar pattern of results was found among children aged 18 months or older. Although children with previous invasive *H influenzae* type b disease do not respond as vigorously to conjugate vaccine as do previously healthy controls, the response is sufficient to justify routine immunization of such children.

(*AJDC* 1989;143:31-33)

Haemophilus influenzae type b is the major cause of sepsis and meningitis in children less than 5 years of age. Immunization with polyribosylribitol phosphate (PRP), the capsular polysaccharide of the organism,

See also p 28.

has been demonstrated to protect against invasive disease in children over 2 years of age.[1] However, response to the vaccine in children less than 2 years old is weak or absent.[2] Similarly, immunologic response to invasive *Haemophilus* disease in this age group is poor[3]; occasionally, such children develop recurrent disease.[4] Furthermore, attempts to immunize infants with PRP vaccine after invasive disease have resulted in poor antibody response.[5]

Currently, studies are under way to extend protection against *H influenzae* type b disease to infants by immunizing them with various conjugate vaccines consisting of PRP linked to a large protein (for example, diphtheria toxoid). When administered to infants, *H influenzae* type b conjugate vaccines have demonstrated enhanced antibody responses and significant protective efficacy as compared with PRP vaccine.[6-11]

The response of children to conjugate vaccine administered after invasive *H influenzae* type b disease has not been reported, to our knowledge. The purpose of this study was to determine whether children who developed invasive *H influenzae* type b disease differed in their response to *H influenzae* type b conjugate vaccines than did children of comparable age with no history of invasive *H influenzae* type b disease.

SUBJECTS AND METHODS

Populations

The study population was recruited from children with culture-proven invasive *H influenzae* type b disease (positive cultures from blood, cerebrospinal fluid, joint aspirate, or pleural fluid) admitted to the Children's Hospital of Vanderbilt University Medical Center, Nashville, Tenn. All 15 children enrolled in the study group were treated at the time of diagnosis with ten to 14 days of appropriate parenteral antibiotics and received recommended rifampin chemoprophylaxis.[12]

All children between the ages of 6 and 24 months without a history of invasive *H influenzae* type b disease or immunization against *H influenzae* type b were recruited from the Vaccine Clinic at the Children's Hospital of Vanderbilt between April 15, 1986, and Jan 8, 1987. Thirty-one such children were immunized and provided appropriate specimens as described below; they constitute the normal control group.

Informed consent for participation in the study was obtained from the parent(s) of each enrolled child.

Immunization

Children in the study and normal control groups were immunized with a conjugate vaccine (Praxis Biologics, Rochester, NY) consisting of *H influenzae* type b oligosaccharide (10 μg) covalently linked to the mutant diphtheria toxoid CRM197 (25 μg).[13]

Each child in the study group received a dose of the conjugate vaccine at the first postdischarge visit. Each child in the normal control group received a dose of the vaccine at the time of recruitment. Any child under the age of 18 months at the time of first vaccination received a second dose of vaccine. For these children, the mean interval between doses was 59 days in the study group and 70 days in the normal control group.

Collection of Specimens

Initial serum specimens were drawn at the time of first immunization. For those children 18 months or older, a second serum specimen was obtained a mean of 65 days (study group) or 64 days (normal control group) thereafter. For children younger than 18 months, a second serum specimen was obtained at the time the subject received the second dose of vaccine, and a third specimen was obtained a mean of 38 days (study group) or 40 days (normal control group) later.

A one-year follow-up serum specimen was obtained from 11 children in the study group and 27 children in the normal control group; these specimens were obtained a mean of 386 days and 384 days, respectively, after first immunization.

Urine specimens were obtained from children in the study group before discharge.

Assays

Serum anti-PRP antibody was detected with a Farr-type radioimmunoassay with the use of intrinsically labeled PRP pro-

Accepted for publication Aug 16, 1988.

From the Divisions of Infectious Diseases, Departments of Pediatrics (Drs Edwards and Porch, Mss Palmer and Bradley) and Medicine (Dr Decker), and the Department of Preventive Medicine (Dr Decker), Vanderbilt University School of Medicine, Nashville, Tenn.

Reprint requests to Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, TN 37232 (Dr Edwards).

Table 1.—Geometric Mean Antibody Titers to Polyribosylribitol Phosphate in Children Younger Than 18 Months*

	Titer, mg/L			
	Before Immunization	After 1st Immunization†	After 2nd Immunization‡	1 y After Immunization§
Study children with previous *Haemophilus influenzae* type b disease‖	0.09 (1/12)	0.74 (5/12)	4.45 (7/12)	6.04 (8/8)
95% confidence limits	0.04-0.17	0.26-2.07	0.83-23.91	2.30-12.15
Controls¶	0.11 (0/16)	3.58 (14/16)	63.50 (16/16)	4.53 (13/14)
95% confidence limits	0.07-0.16	1.72-7.44	34.60-116.53	2.86-7.18

*Numbers in parentheses are proportions of all tested subjects with titers of 1 mg/L or greater.
†$P = .01$.
‡$P = .001$.
§Difference not significant.
‖After first immunization vs before immunization, $P = .0002$; after second vs after first, $P = .01$; one year vs after second, not significant; one year vs after first, $P = .04$.
¶After first immunization vs before immunization, $P < .0001$; after second vs after first, $P < .0001$; one year vs after second, $P < .0001$; one year vs after first, not significant.

Table 2.—Geometric Mean Antibody Titers to Polyribosylribitol Phosphate in Children 18 Months or Older*

	Titer, mg/L		
	Before Immunization	After Immunization†	1 y After Immunization‡
Study children with previous *Haemophilus influenzae* type b disease§	0.07 (0/3)	0.93 (2/3)	0.94 (1/3)
95% confidence limits	0.01-0.63	0.02-50.68	0.02-51.10
Controls‖	0.12 (0/15)	9.69 (14/15)	4.76 (12/13)
95% confidence limits	0.09-0.17	3.96-23.75	2.11-10.73

*Numbers in parentheses are proportions of all tested subjects with titers of 1 mg/L or greater.
†$P = .03$.
‡$P = .09$.
§After immunization vs before immunization titers, $P = .02$; one year vs one month after immunization, not significant.
‖After immunization vs before immunization titers, $P < .0001$; one year vs one month after immunization, not significant.

vided by Porter Anderson, PhD, University of Rochester (NY).[14]

Free PRP antigen in urine was measured by slide latex (Bactigen) agglutination on samples obtained before discharge in the study population.

Statistical Methods

All statistical calculations were performed on logarithmically transformed data.[15] For each appropriate group, geometric mean titers (GMTs), SEs, and 95% confidence intervals were calculated.[16] Within groups, GMT ratios (post/pre) were calculated by dividing the sum of the individual geometric titer ratios by the number of subjects, then determining the antilogarithm; SEs and 95% confidence intervals were calculated as above. Between-group comparisons were made by means of the *t* test for independent samples (*t* test); within-group comparisons were made by means of the *t* test and/or the paired *t* test, as indicated.[17]

RESULTS

Children Younger Than 18 Months

Twelve study children and 16 normal control children were less than 18 months of age at the time of first immunization and therefore received two doses of vaccine. The mean age at the time of first immunization was 345 days for the 12 study children and 325 days for the 16 normal control children. Neither the ages nor the preimmunization GMTs differed significantly between the study and control children. At the first postimmunization visit, antibody titers in the study children had risen from 0.09 to 0.74 mg/L ($P = .0002$), whereas antibody titers in the normal control children had risen from 0.11 to 3.58 mg/L ($P < .0001$) (Table 1). The postimmunization titers differed significantly between the two groups ($P = .01$).

After the second immunization, the mean level of antibody to PRP among the study children increased further to 4.45 mg/L, a value significantly higher than that found after the first immunization ($P = .01$). Once again, however, the normal control children manifested an even greater increase in antibody: after the second immunization, their antibody titer was 63.50 mg/L ($P < .0001$; compared with the value after second immunization for the study group, $P = .001$).

Serum obtained one year after first immunization was available for eight of the study subjects and 14 of the control subjects. Among the study children, the level of mean antibody to PRP had risen to 6.04 mg/L, whereas among the control children it had declined to 4.53 mg/L. These values did not significantly differ.

It is of interest that the GMT after two injections among the study children was 4.45 mg/L, a value that was not significantly different from the 3.58 mg/L achieved after one injection in the normal control children.

Children 18 Months or Older

Three study children and 15 control children were 18 months or older at the time of first immunization and therefore received only one dose of vaccine. Again, neither the ages nor the preimmunization GMTs differed significantly between the study and control children. The preimmunization GMT in the study children was 0.07 mg/L and rose to 0.93 mg/L at the postimmunization visit ($P = .02$) (Table 2). For the 15 control children, the preimmunization GMT was 0.12 mg/L and rose to 9.69 mg/L at the postimmunization visit ($P < .0001$). As was seen for the children under 18 months, the preimmunization GMTs did not differ significantly between the study and normal control groups, whereas the postimmunization GMTs were significantly greater in the control group than in the study group ($P = .03$).

Serum obtained one year after immunization was available for the three study children and for 13 normal control children. The GMT for the study children at one year was 0.94 mg/L, and for the control children, 4.76 mg/L ($P = .09$).

Comparisons Between Age Groups

The antibody responses of the children younger than 18 months and those 18 months or older were compared. No significant differences were noted in the preimmunization GMTs between the two age groups in either the study group or the normal control group.

Among the normal control children, the GMT in the older children after one dose of vaccine was 9.69 mg/L, whereas the GMT in the younger children after one dose was 3.58 mg/L ($P = .07$). The second injection given to the younger control children resulted in a mean titer of 63.50 mg/L, significantly higher than the 9.69 mg/L seen after the one dose given to the older children ($P = .001$). However, one year after vaccination, the GMT in both age groups had declined to nearly identical levels of 4.53 and 4.76 mg/L, respectively.

For the study children, the level of PRP antibody among the younger children was slightly lower after the first immunization than among the older children but was considerably higher after their second immunization; due to the small number of older study children, these differences were not statistically significant. One year after first immunization, there had been no further increase in titer among the older children, whereas the titer among the younger children had risen to 6.04 mg/L ($P = .03$).

Antigen Detection

No free PRP antigen was detected by slide latex agglutination assays of urine collected at the time of discharge from children with invasive *H influenzae* type b disease.

COMMENT

As early as the 1930s, it was known that antibody to the capsular polysaccharide of the *H influenzae* type b organism protected individuals from invasive disease.[18] However, administration of capsular polysaccharide to children less than 2 years of age did not induce an antibody response and was not associated with protection against invasive *H influenzae* type b disease.[1,2] Since the majority of *H influenzae* type b disease occurred in these young children, a more effective vaccine was sought.

The covalent binding of the *H influenzae* type b capsular polysaccharide to a protein results in enhanced antibody response to the capsular polysaccharide in animals and humans.[19] Conjugate vaccines coupling *H influenzae* type b polysaccharide with diphtheria toxoid have been produced and have been demonstrated to be immunogenic and efficacious in young children.[6-9] One such product was recently licensed and recommended for routine immunization of children 18 to 60 months of age.[20]

Previous reports have demonstrated a lack of antibody response to the *H influenzae* type b polysaccharide in children recovering from invasive disease,[3] instances of recurrent *H influenzae* type b disease in children,[4] and the lack of an antibody response to polysaccharide vaccine after recovery from invasive *H influenzae* type b disease.[5] Our data indicate that a more immunogenic antigen preparation is able to overcome at least partially this reduced responsiveness, resulting in the production of antibody at a level generally thought to confer protection from subsequent invasive disease. Furthermore, persistent levels of antibody were demonstrated in immunized study children one year after disease; among the children receiving two immunizations, these levels exceeded those seen in immunized normal control children.

On the basis of these findings, we recommend that previously unimmunized children who have experienced invasive *H influenzae* type b disease be immunized with conjugate vaccine. Children under 18 months of age should receive two doses of vaccine, and children 18 months or older should receive at least one dose.

This study was supported in part by contract AI-02645 from the National Institute of Allergy and Infectious Diseases, Bethesda, Md, and by funds from Praxis Biologics.

We thank Porter Anderson, PhD, for ongoing provision of assay materials and Diana Burns for secretarial assistance.

References

1. Peltola H, Kayhty H, Virtanen M, et al: Prevention of *Hemophilus influenzae* type b bacteremic infections with the capsular polysaccharide vaccine. *N Engl J Med* 1984;310:1561-1566.

2. Smith DH, Peter G, Ingram DL, et al: Responses of children immunized with the capsular polysaccharide of *Haemophilus influenzae* type b. *Pediatrics* 1973;52:637-645.

3. Norden C, Michaels R, Melish M: Serologic responses of children with meningitis due to *Haemophilus influenzae* type b. *J Infect Dis* 1976;134:195-199.

4. Edmondson MB, Granoff D, Barenkamp S, et al: Outer membrane protein subtypes and investigation of recurrent *Haemophilus influenzae* type b disease. *J Pediatr* 1982;100:202-208.

5. Norden C, Michaels R, Melsih H: Effect of previous infection on antibody response of children to vaccination with capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis* 1975;132:69-74.

6. Lepow M, Samuelson J, Gordon L: Safety and immunogenicity of *Haemophilus influenzae* type b–polysaccharide diphtheria toxoid conjugate vaccine in infants 9 to 15 months of age. *J Pediatr* 1985;106:185-189.

7. Anderson P, Pichichero M, Insel R: Immunization of 2-month old infants with protein coupled oligosaccharides derived from the capsule of *Haemophilus influenzae* type b. *J Pediatr* 1985;107:346-351.

8. Anderson P, Pichichero M, Edwards K, et al: Priming and induction of *Haemophilus influenzae* type b capsular antibodies in early infancy by Dpo20, an oligosaccharide-protein conjugate vaccine. *J Pediatr* 1987;111:644-650.

9. Eskola J, Peltola H, Takala AK, et al: Efficacy of *Haemophilus influenzae* type b polysaccharide–diphtheria toxoid conjugate vaccine in infancy. *N Engl J Med* 1987;317:716-722.

10. Einhorn MS, Weinberg GA, Anderson EL, et al: Immunogenicity in infants of *Haemophilus influenzae* type b polysaccharide in a conjugate vaccine with *Neisseria meningitidis* outer-membrane protein. *Lancet* 1986;2:299-302.

11. Weinberg GA, Einhorn MS, Lenoir AA, et al: Immunologic priming to capsular polysaccharide in infants immunized with *Haemophilus influenzae* type b polysaccharide–*Neisseria meningitidis* outer membrane protein conjugate vaccine. *J Pediatr* 1987;111:22-27.

12. American Academy of Pediatrics, Committee on Infectious Diseases: Revision of recommendation for use of rifampin prophylaxis of contacts of patients with *Haemophilus influenzae* infection. *Pediatrics* 1984;74:301-302.

13. Anderson P, Pichichero ME, Insel RA: Immunogens consisting of oligosaccharides from the capsule of *Haemophilus influenzae* type b coupled to diphtheria toxoid or CRM 197. *J Clin Invest* 1985;76:52-59.

14. Anderson P: Intrinsic tritium labeling of the capsular polysaccharide antigen of *Haemophilus influenzae* type b. *J Immunol* 1978; 120:866-870.

15. Armitage P: *Statistical Methods in Medical Research*. New York, John Wiley & Sons Inc, 1971, pp 442-456.

16. White C: Statistical methods in serum surveys, in Paul JR, White C (eds): *Serologic Epidemiology*. Orlando, Fla, Academic Press Inc, 1973, pp 19-32.

17. Colton T: *Statistics in Medicine*. Boston, Little Brown & Co Inc, 1974, pp 131-142.

18. Fothergill LD, Wright J: Influenzal meningitis: The relation of age incidence to the bactericidal power of the blood against the causal organism. *J Immunol* 1933;24:273-284.

19. Anderson P, Insel R, Farsad R, et al: Immunogenicity of 'aggregated PRP,' 'PRP-complex,' and covalent conjugates of PRP with a diphtheria toxoid, in Sell SH, Wright PF (eds): *Haemophilus influenzae: Epidemiology, Immunology, and Prevention of Disease*. New York, Elsevier Science Publishing Co Inc, 1982, pp 275-284.

20. Recommendations of the immunization practices advisory committee (ACIP): Update: Prevention of *Haemophilus influenzae* type b disease. *MMWR* 1988;37:13-16.

Epidemic Methicillin-Gentamicin–Resistant *Staphylococcus aureus* in a Neonatal Intensive Care Unit

Annette C. Reboli, MD; Joseph F. John, Jr, MD; Abner H. Levkoff, MD

• Between October 1985 and August 1986, 49 isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) were obtained from 26 neonates in the neonatal intensive care unit (NICU) at the Medical University Hospital, Charleston, SC. Sites of MRSA isolation were the respiratory tract (33%); nasopharynx (12%); gastrointestinal tract (12%); eye (8%); blood (6%); and catheter tips, wounds, or umbilicus (29%). Very low birth weight was a significant risk factor for MRSA acquisition. All isolates had the same phage type (47/54/75/83A), antibiogram, and whole-cell protein profile. Agarose gel electrophoresis of all 49 isolates disclosed a plasmid level of approximately 45 × 106 daltons (45 megadaltons) in ten different isolates and no plasmid DNA in 39 isolates. Cultures of NICU personnel failed to disclose MRSA carriers and environmental cultures for MRSA were negative. Ten selected isolates showed lower minimal bactericidal concentrations for hexachlorophene than for chlorhexidine. Standard infection-control measures such as contact isolation, hand washing with chlorhexidine, and cohorting (when possible) failed to contain the epidemic. Ultimately, eradication of MRSA from the NICU was associated with the institution of hexachlorophene hand washing.

(*AJDC* 1989;143:34-39)

Accepted for publication Sept 27, 1988.

From the Infectious Diseases Division, Department of Medicine (Drs Reboli and John), and the Department of Medicine, Division of Neonatology, Department of Pediatrics (Dr Levkoff), Medical University of South Carolina, Charleston; and the Veterans Administration Medical Center (Dr John), Charleston. Dr Reboli is now with Hahnemann University, Philadelphia.

Presented in part at the 87th Annual Meeting of the American Society for Microbiology, Atlanta, March 4, 1987.

Reprint requests to Hahnemann University, Infectious Diseases Division, Broad and Vine streets, Philadelphia, PA 19102-1192 (Dr Reboli).

Although *Staphylococcus aureus* is the most frequently reported pathogen causing nosocomial infections in infants and children,[1] methicillin-resistant *S aureus* (MRSA) has been reported infrequently in hospitalized pediatric patients. There have been only three outbreaks of MRSA reported from neonatal intensive care units (NICUs) in the United States[2-4] and four outbreaks reported from Europe and Australia.[5-8] In some of these reports, patient risk factors for MRSA acquisition or the impact of infection control measures were examined. Previous pediatric studies have not investigated the molecular epidemiology of the organism. A recent outbreak of MRSA in the NICU of our university hospital presented the opportunity to study risk factors for MRSA acquisition and the effects of infection control measures, as well as the molecular epidemiology of the epidemic strain.

PATIENTS AND METHODS

Description of the Outbreak

Between October 1985 and August 1986, there was an outbreak of MRSA in the NICU of the Medical University Hospital (MUH), Charleston, SC. During this time, there were 49 isolates of MRSA obtained from 26 neonates. There are approximately 700 admissions annually to this level-3 nursery, approximately 70% of which are infants born at MUH and 30% are infants transferred from hospitals throughout South Carolina. There are three intensive care modules, each with four incubators, and two intermediate modules, each with nine incubators. There is a separate room for putting on gowns at the entrance to the unit. There are ten sinks throughout. The nurse-to-patient ratio is 1:2 in the intensive care part of the unit and 1:4 in the intermediate care section. Physicians and respiratory therapists care for all of the infants. Nurses rotate between intensive and intermediate care modules. The standard antibiotic therapy for suspected sepsis is ampicillin and gentamicin.

In October 1985, the index infant with MRSA was transferred from the NICU of another South Carolina hospital where there was a known outbreak of MRSA. A review of microbiology laboratory records showed that in the five years preceding October 1985, there were no MRSA isolates from the MUH NICU. In August 1986 the outbreak ended; in September and October no MRSA isolates were obtained. In November 1986 an infant born at another institution who was colonized with MRSA was admitted to the NICU, but no spread of the organism was evident. There were no MRSA isolates obtained in December 1986 and January 1987, and only a few sporadic cases were discovered in the 15 months that followed.

Methods

Staphylococcus aureus isolates identified as methicillin-resistant by oxacillin disk (4 μg) from the Clinical Microbiology Laboratory were stored at −70°C in Mueller-Hinton broth containing glycerol and 8 mg/L of methicillin. Identity as *S aureus* was reconfirmed by Gram's staining, the slide coagulase test (BBL, Cockeysville, Md), the catalase test, and deoxyribonuclease production. *Staphylococcus aureus* strains were confirmed as being MRSA when they produced bright orange colonies on *Staphylococcus* 110 agar (S110) (Difco Labs, Detroit) containing 15 μg of methicillin. Further antibiotic susceptibility testing was performed by the disk-diffusion method of Bauer et al[9] and specimens were incubated at 30°C for 24 hours.

Tube dilution susceptibilities to 3% hexachlorophene and 4% chlorhexidine were performed for isolates from ten different neonates using an inoculum of 10^6 bacteria per milliliter of Mueller-Hinton broth. Sixteen concentrations of hexachlorophene and

Table 1.—Clinical Features of High-Risk Neonates Infected with Methicillin-Resistant *Staphylococcus aureus**

Patient No.	Birth Weight, g	Ventilatory Support	Diagnosis	MRSA Infection	Treatment	Outcome
1	1580	Yes	BPD; *Candida* sepsis; chronic CHF; CHD; NE; renal failure; seizure disorder	Pneumonia	Vancomycin	Resolution but died with CHF
2	880	Yes	*Candida* sepsis; *Escherichia coli* UTI; hepatic dysfunction; HMD; IVH; NE; PDA; RF; rickets	Pneumonia	Vancomycin	Resolution but died of *Candida* sepsis
3	1330	Yes	Hypoglycemia; PDA; renal insufficiency; respiratory distress	Conjunctivitis	Bacitracin	Resolution; survived
4	1360	Yes	BPD; HMD; hydrocephalus; IVH; PDA; RF	Umbilical wound infection	Bacitracin; local care	Resolution; survived
5	2210	Yes	Respiratory distress	Conjunctivitis	Bacitracin	Resolution; survived
6	710	Yes	BPD; HMD; hypoglycemia; IVH; PDA	Bacteremia; pneumonia	Vancomycin	Resolution; survived
7	910	Yes	BPD; cleft palate; *Escherichia coli* sepsis; hydrocephalus; IVH; PDA; RF	Pneumonia with sepsis	Vancomycin	Resolution; survived
8	1180	Yes	BPD; HMD; hyperglycemia; PDA	Bacteremia	Vancomycin	Resolution; survived
9	1588	Yes	HMD; NE; perforated ileum; peritonitis	Abdominal surgical wound infection	Vancomycin; drainage	Resolution; survived
10	760	Yes	BPD; hepatitis; HMD; IVH; RF	Wound infection; bacteremia	Vancomycin; drainage	Resolution; survived
11	1380	Yes	*Candida* sepsis; centronuclear myopathy; HMD	Soft-tissue abscess	Vancomycin; drainage	Resolution but died of cardiopulmonary arrest

*MRSA indicates methicillin-resistant *Staphylococcus aureus* infection; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CHF, congestive heart failure; HMD, hyaline membrane disease; IVH, intraventricular hemorrhage; NE, necrotizing enterocolitis; PDA, patent ductus arteriosus; RF, retrolental fibroplasia; and UTI, urinary tract infection.

Table 2.—Comparison of Birth Weights for Neonates With and Without MRSA in the NICU*

Birth Weight	Neonates With MRSA (n=26)	Neonates Without MRSA (n=630)
<1000 g, No. (%) of infants	13 (50)	51 (8)
>1000 g, No. (%) of infants	13 (50)	579 (92)
>1500 g, No. (%) of infants	6 (23)	508 (81)
Mean, g	1317	2367

*MRSA indicates methicillin-resistant *Staphylococcus aureus* infection; NICU, neonatal intensive care unit.

†$P<.000001$ as determined by two-sample t test.

chlorhexidine ranging from 0.3 mg/L to 10 000 mg/L were tested. The tubes were incubated at 30°C for 24 hours, and then 0.001 mL from each tube was plated on blood agar and incubated at 30°C for 24 hours. The first dilution that showed less than two colonies was considered the minimal bactericidal concentration (MBC).

Data that included birth weight, sex, race, leukopenia (defined as a white blood cell count $<5.0\times10^9$/L), use of a ventilator, length of hospital stay, and outcome from all infants admitted to the NICU during the outbreak were collected and stored for comparison by computer. Medical records of all infants with MRSA were reviewed to determine whether the infants were infected or colonized. Infection was defined as the presence of MRSA with clinical symptoms and signs, or a positive culture from a normally sterile body fluid.

Molecular Studies.—The plasmid content of all 49 isolates was determined by a modification of the method of Hansen and Olsen,[10] electrophoresis was performed on a 0.7% agarose gel, specimens were stained with ethidium bromide, and the specimens were then photographed. Plasmid size was determined by comparison with DNA standards of known molecular weight using a linear regression model.[11] Filter mating was attempted by a modification of the method of McHugh et al[12] using a plasmid-free, sulfonamide-resistant, methicillin-gentamicin–sensitive strain of *S aureus* as the recipi-

ent. A control MRSA strain with a transferable 33-megadalton (MDa) plasmid that confers gentamicin resistance was also tested. Dilutions of the filter-mated bacteria were streaked onto selective media containing methicillin and sulfamethoxazole or gentamicin and sulfamethoxazole.

Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) of whole-cell preparations was performed by the method of Laemmeli.[13] Isolates were streaked onto blood agar and incubated at 30°C overnight. A few colonies were inoculated into 50 μL of luria broth and incubated at 37°C for three hours in air. Fifty microliters of lysostaphin (0.4 mg/mL of 10 mmol/L TRIS; pH 8.0) was added to each sample and incubated at 37°C for 45 minutes. Each sample was mixed with 100 μL of double-strength buffer (0.5 mol/L TRIS; pH 6.8; 10% SDS, glycerol, β-mercaptoethanol, distilled water, and bromophenol blue) and boiled for five minutes; then 15 μL of each sample was loaded onto a 4.5% stacking gel and electrophoresis was performed at 40 mA. Amperage was increased to 80 mA for electrophoresis through a 10% separating gel. Gels were stained with silver (Bio-Rad, Richmond, Calif).

Bacteriophage typing of MRSA strains was performed with standard typing phages at routine test dilution and × 100 routine test dilution at the Michigan Department of Public Health (Houghton, Mich).[14]

Epidemiologic Studies.—The MRSA outbreak in the NICU was first suspected when one of us (A.C.R.) began to monitor MRSA activity in MUH as part of another study. When it became apparent there was a problem with MRSA in the NICU, cultures of the nares, pharynx, or endotracheal tubes of each infant were obtained weekly. During the last few months of the outbreak, cultures of the umbilicus were obtained weekly. Screening cultures of the nares of 22 members of the nursing staff, seven physicians, and four respiratory therapists were obtained on five separate occasions using sterile cotton-tipped applicators moistened in saline solution and rotated ten times around the right and left anterior nares. The applicators were streaked immediately onto *Staphylococcus* 110 agar (S110) (Difco Labs) without and with methicillin (15 mg/L) and the cultures were incubated at 30°C for 72 hours. Environmental cultures were done with S110 agar settle plates without and with methicillin left open to room air for one half hour.

The two-sample t test[15] was used to compare mean birth weights of infants with MRSA and infants without MRSA, mean birth weights of MRSA-infected and MRSA-colonized infants, and mean lengths of stay of infants with and without MRSA. Other variables were compared using the χ^2 test.[16]

Table 3.—Comparison of Characteristics of Neonates With and Without MRSA*

Characteristic	No. (%) of Patients: Neonates With MRSA (n=26)	Neonates Without MRSA (n=593)
Leukopenia†	1 (3.8)	9 (1.5)
Use of Ventilator‡	21 (80.7)	179 (30)
Male Sex§	17 (65)	320 (53.9)
Female Sex	9 (34.6)	273 (46)
White Race‖	13 (50)	274 (46)
Non-white Race	13 (50)	319 (54)
Death¶	4 (15.3)	63 (10.6)

*MRSA indicates methicillin-resistant *Staphylococcus aureus* infection.
†$\chi^2 = 0.85$; $P = .36$.
‡$\chi^2 = 29.14$; $P < .0001$.
§$\chi^2 = 1.31$; $P = .25$.
‖$\chi^2 = 0.14$; $P = .7$.
¶$\chi^2 = 0.58$; $P = .44$.

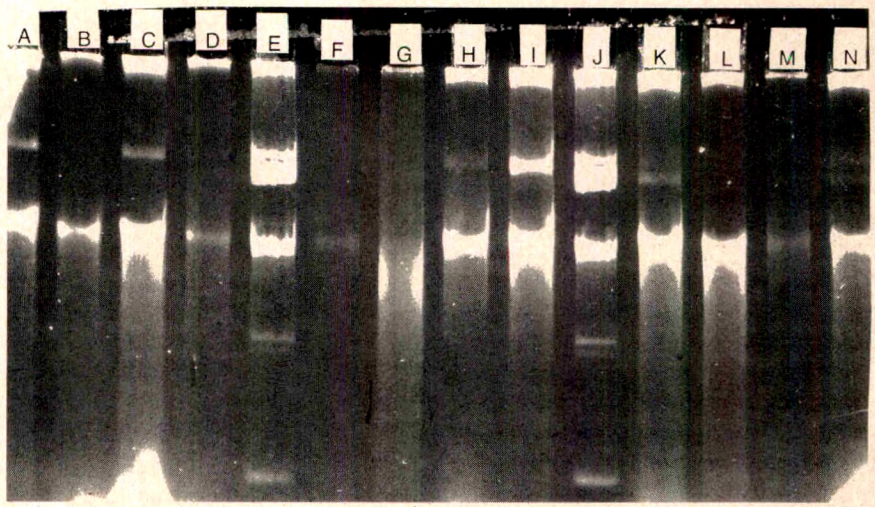


Fig 1.—Agarose gel electrophoresis of plasmid DNA prepared from epidemic methicillin-resistant *Staphylococcus aureus* isolates. Lanes E and J are controls of known molecular weight; lanes A, C, H, and I show 45-megadalton (MDa) plasmid. In lanes K and N there is 33-MDa plasmid along with 45-MDa plasmid. Lanes B, D, F, G, L, and M have no visible plasmids. Chromosomal DNA band is present in each isolate.

RESULTS

Sites of MRSA isolation included the respiratory tract (33%); nasopharynx (12%); gastrointestinal tract (12%); eye (6%); blood (6%); and umbilicus, wounds, or catheter tips (29%).

Twenty-five of the 26 infants with MRSA were premature. Twenty were born at MUH and six were transferred from other hospitals. All had received antibiotics previously (usually ampicillin and gentamicin). Fifty-eight percent were colonized and 42% were infected with MRSA and were treated with vancomycin or bacitracin. Clinical features of the 11 infants with MRSA infection are shown in Table 1. All of these infected infants had similar underlying diseases that were similiar to those of the 15 infants who were judged to be colonized with MRSA, and all required mechanical ventilatory support. The most common MRSA infections were pneumonia (four infants) and bacteremia (three infants). Three patients had wound infections, two had conjunctivitis, and one had a soft-tissue abscess. There was no statistically significant difference in birth weight between MRSA-infected and MRSA-colonized infants. Of the four infants from whom MRSA was isolated and who died, three had MRSA infections, but the MRSA

infection was not temporally related to the deaths. The mean length of stay among the 22 infants with MRSA for whom it was available was 84.9 days, compared with 19.3 days for a control group of 888 infants in the NICU who were without MRSA colonization or infection ($P<.0001$). Methicillin-resistant *S aureus* was cultured from 75% of the infants within two weeks of admission.

Table 2 shows a comparison of birth weights of infants colonized or infected with MRSA and those not colonized or infected. Of the 26 with MRSA, 50% weighed less than 1000 g and 50% weighed more than 1000 g. Only six infants (23%) weighed more than 1500 g. Of the control group of 630 infants without MRSA who were admitted to the NICU during the same time period, 8% weighed less than 1000 g and 92% weighed more than 1000 g. Five hundred eight infants (81%) weighed more than 1500 g. The mean birth weight of the infants with MRSA was 1317 g; for infants without MRSA it was 2367 g ($P<.000001$). A comparison of other characteristics of neonates colonized or infected with MRSA and those not colonized or infected is shown in Table 3. Use of a ventilator was not an independent risk factor but rather was related to low birth weight.

All isolates had the same antibiograms that showed susceptibility to amikacin, chloramphenicol, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin; the antibiograms showed resistance to amoxicillin–clavulanic acid, cephalothin, clindamycin, erythromycin, gentamicin, methicillin, oxacillin, penicillin, and tobramycin. For the ten isolates tested, the mean MBC of chlorhexidine was 7.7 mg/L, with a range of 4.8 to 9.75 mg/L; the mean MBC of hexachlorophene was 2.16 mg/L, with a range of 1.22 to 2.4 mg/L. There are no published bactericidal break points for these soaps. There was no difference in MBCs between plasmid-bearing and plasmid-free isolates.

Molecular Studies.—There was a plasmid of 45 MDa in ten of the 49 neonatal MRSA isolates examined (Fig 1). These plasmid-bearing isolates occurred during the last three months of the outbreak. Along with this large plasmid, a plasmid of 33 MDa was present in two isolates. No other plasmids were visualized. The 45-MDa plasmid and the 33-MDa plasmid from the outbreak strain were not transferable, but the control 33-MDa gentamicin R-plasmid was transferable in filter mating experiments.

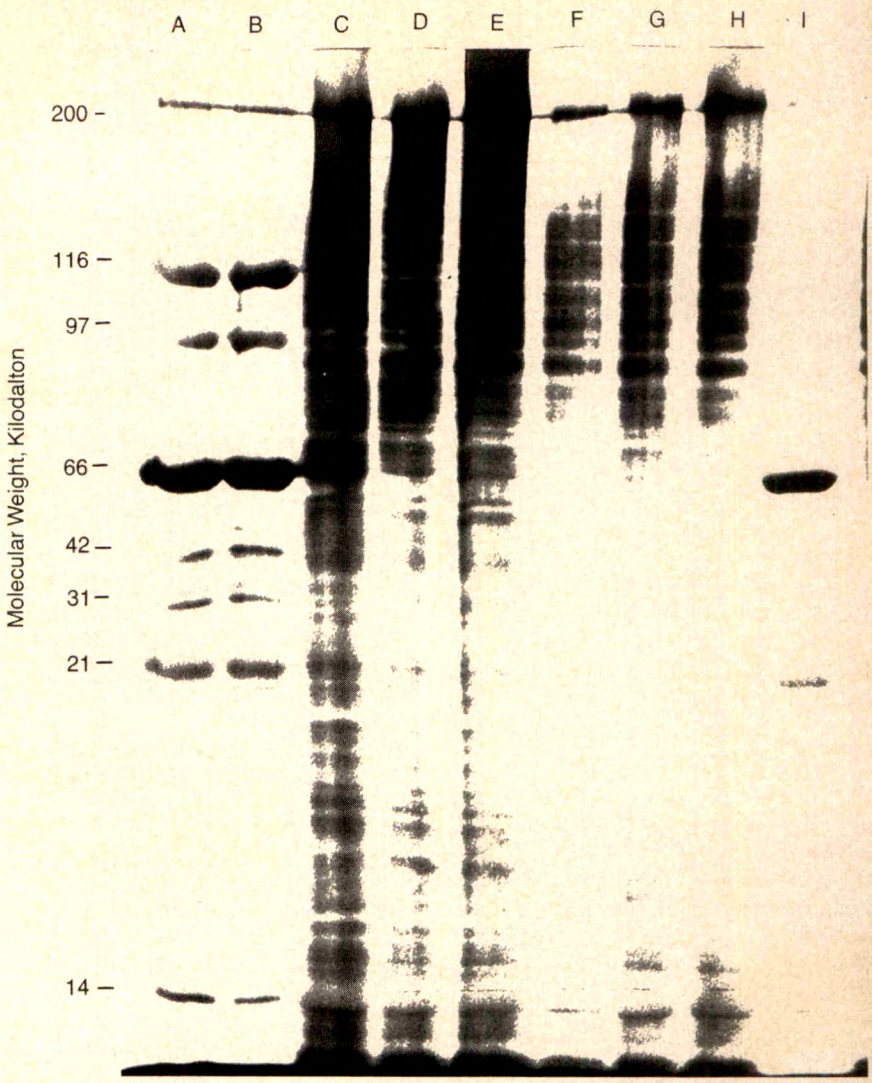


Fig 2.—Sodium dodecyl sulfate polyacrylamide gel electrophoresis of whole-cell protein preparations from epidemic methicillin-resistant *Staphylococcus aureus* isolates. Gel has been stained with silver. Lanes A and B show standard high-molecular-weight markers. Lane I shows standard low-molecular-weight markers. Lanes C through H are isolates of methicillin-resistant *Staphylococcus aureus* from epidemic. Gel demonstrates homogeneity of these isolates.

All isolates elaborated identical whole-cell protein profiles with prominent bands at approximately 200, 97, 90, and 31 kilodaltons (Fig 2). These bands were not present in methicillin-sensitive *S aureus* and other MRSA tested (data not shown). All isolates from the outbreak were phage type 47/54/75/83A.

Infection Control Measures.—During the course of the outbreak, several infection control measures were introduced. As soon as an infant was identified as being colonized or infected with MRSA, he or she was put in contact isolation. Strict hand washing with chlorhexidine soap by personnel between their handling of patients was stressed via educational in-services. Personnel were advised to wash their hands and their forearms up to the elbows when entering the nursery and to repeat the procedure before and after handling each infant. Infected or colonized infants were cohorted into one in-

tensive care module when possible. Nurses assigned to this group were not assigned to MRSA-negative infants. Surveillance cultures of the nares of nursing staff, physicians, and respiratory therapists were performed but failed to disclose any carriers. Environmental cultures were also negative. Despite these standard infection control measures, which were implemented in February 1985, the outbreak continued. In mid-July, hand washing by staff members with hexachlorophene soap was instituted. After August 1985, when the last MRSA-colonized infant was discharged, there were no problems with MRSA (Fig 3).

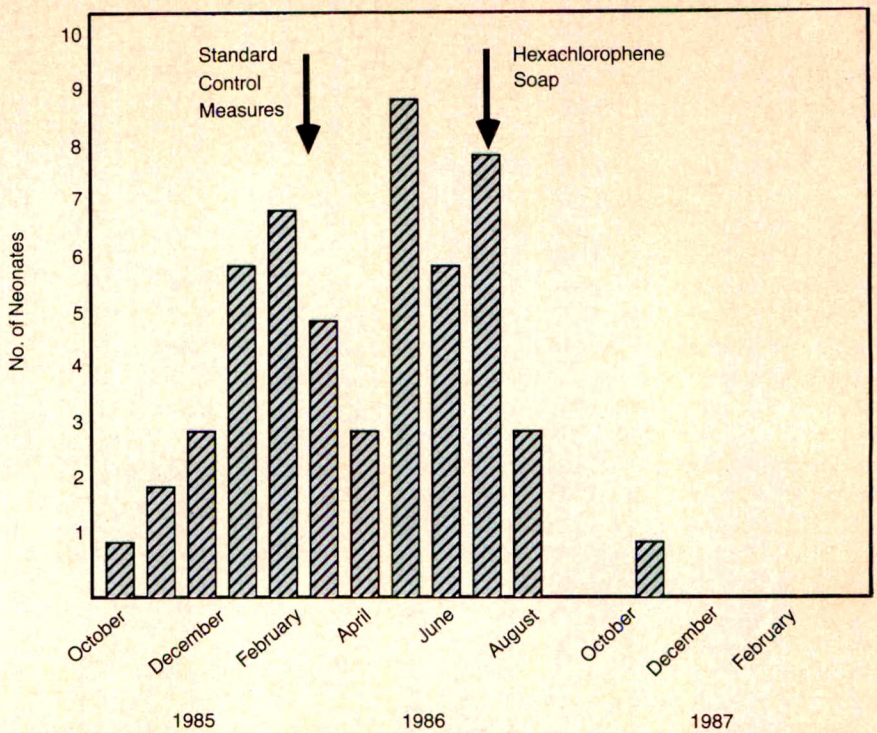


Fig 3.—Histogram of number of neonates colonized or infected with methicillin-resistant *Staphylococcus aureus* per month between October 1985 and February 1987.

COMMENT

Advances in medical technology have improved the survival of infants of very low birth weight, resulting in an increase in NICU bed use by a population that has longer hospital stays and is subject to more invasive procedures and that, therefore, is at greater risk for nosocomial infections.[17-19] Nosocomial infection rates have been shown to be significantly higher in infants with birth weights less than 1500 g.[19,20] In the present study, the infants acquiring MRSA were of very low birth weight, with 50% weighing less than 1000 g. This was the only statistically significant risk factor for MRSA acquisition. Since MRSA is increasing in frequency in acute care children's hospitals in the United States,[21] control of this organism will present a challenge to all physicians who care for high-risk neonates.

Almost all of the infants with MRSA in the outbreak reported herein were premature and all had received prior antibiotic therapy. Forty-two percent had clinical infection and required treatment for MRSA. The percentage of infants who required therapy in our study is higher than the 25% previously reported.[3] Infection or colonization with MRSA did not cause a significant increase in mortality in the present study, perhaps because of the early, generalized use of vancomycin. There was also a decrease in *Staphylococcus epidermidis* and methicillin-sensitive *S aureus* infections during the outbreak (data not shown). The length of hospital stay was significantly longer in the infants with MRSA than in those without it, but this difference probably reflects the very low birth weight of these infants. Indeed, most of the infants with MRSA acquired the organism within two weeks of admission.

The plasmid content of MRSA from NICU outbreaks has not been reported, to our knowledge. Ten of our patients' isolates contained a 45-MDa cryptic plasmid that was acquired during the last few months of the outbreak. Plasmids of various sizes (generally in the 20- to 30-MDa range) have been consistently described in MRSA,[22-27] but never before has a plasmid as large as 45 MDa been reported. A 33-MDa plasmid (present in two of our patients' isolates), which confers gentamicin resistance in MRSA, has been previously described.[25] Since most of our patients' isolates lacked plasmids and since those plasmids that were present were nontransferable, gentamicin resistance in our patients' isolates was presumably chromosomally encoded. Only plasmid-encoded gentamicin resistance has been reported previously in isolates of MRSA from the United States, although gentamicin resistance is usually chromosomally encoded in strains from certain areas of Europe.[23,26]

All of our patients' isolates had the same antibiogram and phage type (47/54/75/83A). An MRSA strain with this phage type has been reported to be the cause of one other neonatal MRSA outbreak.[3] We examined SDS-PAGE as another method for typing MRSA strains.[28] All of our patients' isolates had identical protein profiles, suggesting that SDS-PAGE may be complementary to phage typing, antibiograms, and plasmid analysis in defining the epidemiology of an outbreak. It may be particularly useful in situations such as the one described in the present report, in which most of the MRSA isolates lacked plasmids.

The infection control implications of the present study are intriguing. Standard infection control measures such as contact isolation, cohorting of colonized or infected patients, cohorting of personnel, surveillance cultures of patients, and culturing of personnel to identify carriers[29] were unsuccessful in controlling the epidemic at our institution. Although cultures of the hands of

personnel were not obtained in the present study, hand contact was probably the mode of spread of the organism.

A major finding in the present study was a marked decrease in MRSA activity after changing the antiseptic handwashing soap that health care providers were using from chlorhexidine to hexachlorophene. Similar to our data, other studies have shown relative in vitro resistance to chlorhexidine by MRSA and relative susceptibility to hexachlorophene.[30,31] Such differences in susceptibility to antiseptic soaps may have in vivo importance: a change in soap may be indicated if standard infection control measures fail in containing a staphylococcal outbreak. Antiseptic resistance in MRSA is probably not plasmid mediated, since no differences in susceptibility were seen between the plasmid-bearing and plasmid-free isolates tested. It is also noteworthy that after the last known neonate was discharged, cases appeared only sporadically during the next 15 months.

This study was supported in part by the Veterans Administration.

Dale W. Vance, PhD, Michigan Department of Public Health, Houghton, performed the phage typing; T. Hulsey and Myla Ebeling performed statistical analysis; W. Edmund Farrar, MD, reviewed the manuscript; Lisa Johnson provided technical assistance; and Judy Anderson provided secretarial assistance.

References

1. Jarvis WR: Epidemiology of nosocomial infections in pediatric patients. *Pediatr Infect Dis J* 1987;6:344-351.

2. Graham DR, Correa-Villasenor A, Anderson RL, et al: Epidemic neonatal gentamicin-methicillin-resistant *Staphylococcus aureus* infection associated with nonspecific topical use of gentamicin. *J Pediatr* 1980;97:972-978.

3. Dunkle LM, Naqv SH, MaCallum R, et al: Eradication of epidemic methicillin-gentamicin-resistant *Staphylococcus aureus* in an intensive care nursery. *Am J Med* 1981;70:455-458.

4. Armington LA, Mooney BR: Early recognition and control of methicillin-resistant *Staphylococcus aureus* in a newborn ICU, abstracted. *Am J Infect Control* 1986;14:84.

5. Mulhern B, Griffin E: An epidemic of gentamicin/cloxacillin resistant staphylococcal infection in a neonatal unit. *Irish Med J* 1987;74:228-229.

6. Price EH, Brain A, Dickson JAS: An outbreak of infection with a gentamicin and methicillin-resistant *Staphylococcus aureus* in a neonatal unit. *J Hosp Infect* 1980;1:221-228.

7. Trallero EP, Arenzana JG, Castaneda AA, et al: Unusual multiresistant *Staphylococcus aureus* in a newborn nursery. *AJDC* 1981;135:689-692.

8. Gilbert GL, Asche V, Hewstone AS, et al: Methicillin-resistant *Staphylococcus aureus* in neonatal nurseries. *Med J Aust* 1982;1:455-459.

9. Bauer AW, Kirby WMM, Sherris JC, et al: Antibiotic susceptibility testing by standardized single disc method. *Am J Clin Pathol* 1966;45:493-496.

10. Hansen JB, Olsen RH: Isolation of large bacterial plasmids and characterization of the P2 incompatibility group plasmids p MG1 and p MG5. *J Bacteriol* 1978;135:227-238.

11. John JF Jr, McNeill WF: Characteristics of *Serratia marcescens* containing a plasmid coding for gentamicin-resistance in nosocomial infections. *J Infect Dis* 1981;143:810-817.

12. McHugh GL, Moellering RC, Hopkins CC, et al: *Salmonella typhimurium* resistant to silver nitrate, chloramphenicol, and ampicillin. *Lancet* 1975;1:235-240.

13. Laemmeli UK: Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* 1970;227:680-685.

14. Martin R, Adcock MP, Wentworth BB: Prevalence of *Staphylococcus aureus*, phage type 29/52/80, in Michigan. *Am J Public Health* 1984;74:366-367.

15. Kuzma JW: One-tailed versus two-tailed tests, in Kuzma JW (ed): *Basic Statistics for the Health Sciences*. Palo Alto, Calif, Mayfield Publishing Co, 1984, pp 108-110.

16. Kuzma JW: The chi-square test, in Kuzma JW (ed): *Basic Statistics for the Health Sciences*. Palo Alto, Calif, Mayfield Publishing Co, 1984, pp 141-158.

17. Paneth NM, Kiely JL, Wallenstein S: Newborn intensive care and mortality in low-birthweight infants. *N Engl J Med* 1982;307:149-155.

18. Freeman J, Platt R, Sidebottom DG, et al: Coagulase-negative staphylococcal bacteremia in the changing neonatal intensive care unit population. *JAMA* 1987;258:2548-2552.

19. Goldmann DA, Durbin WA, Freeman J: Nosocomial infections in a neonatal intensive care unit. *J Infect Dis* 1981;144:449-459.

20. Hemming VG, Overall JC, Britt MR: Nosocomial infections in a newborn intensive-care unit. *N Engl J Med* 1976;294:1310-1316.

21. Jarvis WR, Thornsberry C, Boyce J, et al: Methicillin-resistant *Staphylococcus aureus* at children's hospitals in the United States. *Pediatr Infect Dis* 1985;4:651-655.

22. Archer GL, Johnson JL: Self-transmissible plasmids in staphylococci that encode resistance to aminoglycosides. *Antimicrob Agents Chemother* 1983;24:70-77.

23. Cafferkey MT, Coleman D, McGrath B, et al: Methicillin-resistant *Staphylococcus aureus* in Dublin 1971-84. *Lancet* 1985;2:705-708.

24. Coleman DC, Pomeroy H, Estridge JK, et al: Susceptibility to antimicrobial agents and analysis of plasmids in gentamicin- and methicillin-resistant *Staphylococcus aureus* from Dublin hospitals. *J Med Microbiol* 1985;20:157-167.

25. Kozarsky PE, Rimland D, Terry PM, et al: Plasmid analysis of simultaneous nosocomial outbreaks of methicillin-resistant *Staphylococcus aureus*. *Infect Control* 1986;7:577-581.

26. Lyon BR, Skurray R: Antimicrobial resistance of *Staphylococcus aureus*: Genetic basis. *Microbiol Rev* 1987;51:88-134.

27. Rhinehart E, Shlaes DM, Keys TF, et al: Nosocomial clonal dissemination of methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med* 1987;147:521-524.

28. Stephenson JR, Crook SJ, Tabaqchali S: New method for typing *Staphylococcus aureus* resistant to methicillin based on sulphur-35 methionine labelled proteins: Its application in an outbreak. *Br Med J* 1986;293:581-583.

29. Ayliffe GA: Guidelines for the control of epidemic methicillin-resistant *Staphylococcus aureus*. *J Hosp Infect* 1986;7:193-201.

30. Brumfitt W, Dixson S, Hamilton-Miller JMT: Resistance to antiseptics in methicillin and gentamicin resistant *Staphylococcus aureus*. *Lancet* 1985;1:1442-1443.

31. Lacey RW, Barr KW, Barr VE, et al: Properties of methicillin-resistant *Staphylococcus aureus* colonizing patients in a burn unit. *J Hosp Infect* 1986;7:137-148.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Managing Laboratory Information

Charles H. Altshuler, MD (*Arch Pathol Lab Med* 1988;112:1188-1189)

Neonatal Neutrophil Host Defense

Prospects for Immunologic Enhancement During Neonatal Sepsis

Mitchell S. Cairo, MD

• Neonatal host defense simulates a clinical state of immunodeficiency that predisposes the preterm and term newborn to overwhelming bacterial sepsis. There are various immunologic components that are deficient in the newborn and new methods to enhance their function. Defects in both the quantitative and qualitative aspects of the neonatal phagocyte contribute substantially to the immaturity of neonates' immune systems. The neonate lacks an adequate number of granulocyte bone marrow progenitor cells, and has a decreased neutrophil storage pool and an increased tendency to peripheral neutropenia during neonatal sepsis. Additionally, the neonatal granulocyte demonstrates altered physiologic function compared with that found in the adult with respect to chemotaxis, phagocytosis, oxidative metabolism, and bacterial killing. Some recent clinical studies have suggested the benefit of using adult neutrophil transfusions as adjuvant treatment during neonatal bacterial sepsis, yet other studies have found the use of polymorphonuclear neutrophil leukocyte transfusions to be inconclusive. Reduced circulating immunoglobulins and impaired production of specific antibody have also led to recent trials in the use of prophylactic intravenous immunoglobulin in preterm infants predisposed to sepsis. Recently, hematopoietic colony-stimulating factors have been demonstrated to improve in vitro neonatal neutrophil physiologic activity. Future therapy of neonatal sepsis will depend on new nontoxic methods for enhancing neonatal host defense.
(*AJDC* 1989;143:40-46)

Neonatal bacterial sepsis is a life-threatening disorder that occurs in approximately one to ten patients per 1000 live births.[1] The mortality rate from neonatal bacterial sepsis varies between 20% and 75%, depending on the organism, immunocompetency of the host, and associated complications present at diagnosis.[1,2] The final outcome from neonatal sepsis is dependent on numerous factors, including the maturity and immunologic and physiologic status of the neonate at the time of presentation, the presence of perinatal conditions that predispose to infection, and the use of invasive supportive care measures such as vascular catheters. Early diagnosis and early initiation of appropriate antibiotic therapy and the management of metabolic and respiratory problems can greatly affect the outcome of neonatal sepsis.

Neonatal host defenses in the animal and human neonate are immunologically immature and therefore contribute substantially to the high incidence of overwhelming sepsis in preterm and term newborns. The immune system consists of four major components: cell-mediated immunity (T cells); the complement system; antibody-mediated immunity (B cells); and the macrophage/neutrophil phagocytic system. The high incidence of bacterial sepsis in the newborn appears in part to be secondary to immaturity of at least two and maybe more components of the immune system. The two most important deficits that seem to increase the risk of bacterial sepsis are quantitative and qualitative changes in the phagocytic system and defects in antibody-mediated immunity.

Accepted for publication Sept 21, 1988.

From the Division of Neonatalogy and Hematology/Oncology, Childrens Hospital of Orange County, University of California, Irvine.

Reprint requests to Division of Neonatology and Hematology/Oncology, Childrens Hospital of Orange County, 455 S Main, Orange CA 92668 (Dr Cairo).

NEUTROPHIL QUANTITATIVE AND QUALITATIVE DEFICIENCIES

Christensen and Rothstein[3] and others have documented substantial quantitative deficiencies in neonatal rat and human myeloid cells and their ineffective response to bacterial infection (Table 1). Christensen and Rothstein[3] have demonstrated only 10% to 20% of proliferative pools (colony-forming unit–granulocyte macrophage [CFU-GM]) in neonatal rats compared with adult animals. Additionally, despite lower numbers of CFU-GMs found in the newborn rat, their proliferative rate, as assayed by tritiated thymidine suicide studies, is approximately 75% to 80% of maximal levels. This compares with a proliferative rate of only 25% found in adult animals.[3] Similarly, Christensen and colleagues[4] have reported that the CFU-GM proliferative rate found in the peripheral blood of premature humans is also near maximal capacity. Finally, the neutrophil storage pool, consisting of polymorphonuclear neutrophil leukocytes (PMNs), band cells, and metamyelocytes, is also markedly reduced in the premature and newborn rat (25%) compared with adult animals.[5]

After inoculation with group B streptococcus, the newborn rat demonstrates substantially different neutrophil kinetics than are found in adult animals. Adult animals increase their circulating PMN counts by increasing their stem cell pool two to three times and increase their stem cell proliferation rate by a similar amount. In contrast, neonatal animals under the same conditions fail to increase their stem cell pool (CFU-GM), and may in fact decrease this pool. Additionally, neonatal animals also fail to increase their stem cell proliferative

Table 1.—Neonatal Quantitative Animal Myeloid Deficiencies*

	Group	
	Neonatal	Adult
Proliferative pool (CFU-GM), %	10	100
Proliferative rate (tritiated thymidine suicide), %	80	25
Bone marrow neutrophil storage pool (PMNs, band cells, meta), %	25	100
Bone marrow:circulating pool (total PMNs)	2:1	10:1
Response to sepsis (PMN pool)	Decrease	Increase

*CFU-GM indicates colony-forming unit–granulocyte-macrophage; PMNs, polymorphonuclear neutrophil leukocytes.

rate. Subsequently, neonatal animals deplete their already reduced neutrophil storage pool. This development contributes to reduced circulating mature neutrophils and increased mortality during sepsis.[6]

Neutrophil utilization is also greatly accelerated during bacterial infection. In adult rats the daily turnover of neutrophils increases from 1.6×10^9/kg/d to 5×10^9/kg/d and approximates the adult storage pool of neutrophils (6.0×10^9/kg/d). Therefore, an adult animal can consume its entire neutrophil storage pool in one day during bacterial sepsis. Since neonates have an already compromised neutrophil storage pool, this increase in neutrophil utilization that occurs during bacterial sepsis contributes to the exhaustion of neutrophil reserves during neonatal sepsis and subsequently increases their mortality.

During neonatal sepsis, even adequate numbers of PMNs may be insufficient because their ability to function normally may be impaired. Numerous in vitro abnormalities have been demonstrated in neonatal PMNs, especially in times of stress or infection.[7] These abnormalities include decreased deformability, chemotaxis, phagocytosis, C3bi receptor expression, adherence, bacterial killing, and depressed oxidative metabolism.[8-13] Specifically, Miller[8] demonstrated impaired chemotaxis in neonatal neutrophils in response to various bacterial organisms and antigen-antibody complexes. Additionally, Anderson et al[14] demonstrated impaired chemotaxis to f-met-leu-phe (FMLP), C5A desarg, and *Escherichia coli* filtrate. Although phagocytosis has additionally been demonstrated to be abnormal in neonatal phagocytes, it appears that this phenomenon is most likely secondary to decreased opsonic activity rather than an intrinsic defect of the neonatal PMN.[15,16] Bactericidal killing of PMNs from healthy term newborns appears to be normal compared with impaired killing from newborns who are stressed or concurrently infected.[11] Oxidative metabolic abnormalities have been additionally demonstrated in PMNs of newborns. Specific studies of oxidative metabolism suggest a discrepancy between superoxide production and hydroxyl radical generation. Ambruso et al[17,18] reported a decrease in the generation of the hydroxyl radical in PMNs in newborns compared with those in adults. This is in contrast with normal to increased amounts of superoxide generation in PMNs in neonates. Additionally, Shigeoka et al[19] have demonstrated defective oxidative responses from stressed neonatal PMNs compared with PMNs obtained from normal or unstressed newborns. Finally, Bruce et al[20] have recently reported impaired surface membrane expression of C3bi receptors in neonatal neutrophils. This impaired expression of surface membrane receptors (C3bi) has been implicated in the pathogenesis of abnormal adherence of neonatal PMNs.[21]

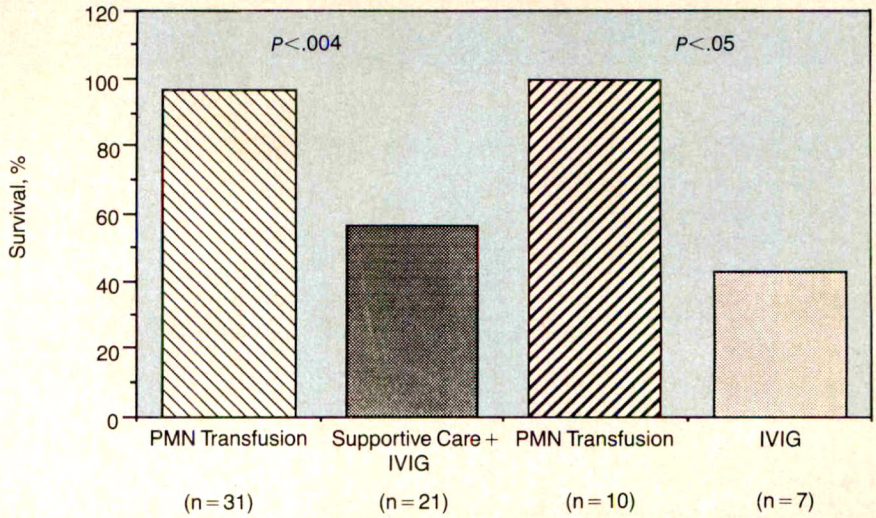
HUMORAL AND OPSONIC DEFICIENCIES

Humoral immunity, ie, quantitative immunoglobulins or opsonic activity, is also markedly impaired in animal and human preterm and term newborns. Preterm and term newborns have poor responses to various antigenic stimuli, reduced levels of gamma globulin at birth, and a reduced maternal supply of immunoglobulin from placental transport. The presence of physiologic hypogammaglobulinemia has been noted by several investigators in preterm and term newborns. Ballow et al[22] have reported reduced levels of IgG in premature infants of 26 to 31 weeks' gestational age. With increasing gestational age, increases in circulating immunoglobulin levels have been noted, but levels are still reduced compared with those in term newborns and infants. Almost 33% of infants with a birth weight less than 1500 g develop substantial hypogammaglobulinemia, with levels of IgG less than 200 mg/dL.[23] Neonates also have low levels of IgA and IgM because of the poor ability of these two immunoglobulins to cross the placenta. Neonates also have lower concentrations of certain IgG subclasses, including IgG2 and IgG4. Neonates, therefore, are unusually susceptible to pyogenic bacterial infections, since most of the antibodies that opsonize capsular polysaccharide antigens of pyogenic bacteria (group B streptococci and *E coli*) are contained in these deficient IgG2 and IgM subfractions.

Neonates, even during overwhelming sepsis, do not produce type-specific antibody. During neonatal sepsis there appears to be a transient increase in the synthesis of IgM but little production of IgG.[24] This impairment in type-specific antibody production appears to be secondary to a defect in the differentiation of B lymphocytes into immunoglobulin-secreting plasma cells and T-lymphocyte mediated facilitation of antibody synthesis.[25,26] Thus, reduced antibody levels in the neonate appear to be secondary to reduced maternal transport of maternally derived antibodies and impaired neonatal antibody production secondary to the abnormal interaction between B and T lymphocytes in the neonate.

Other opsonic and humoral factors are deficient in neonates besides decreased immunoglobulins. In the term neonate, total hemolytic complement activity, which measures the classic complement pathway, constitutes approximately 50% of adult activity. Additionally, complement-dependent opson-

ic activity and generation of chemotactic activity is also depressed in the neonate.[27,28] The activity of the alternative complement pathway, secondary to decreased levels of factor B, is also decreased in the neonate.[29] Finally, fibronectin, a plasma protein that promotes reticuloendothelial clearance of invading microorganisms, is deficient in neonatal cord plasma and the addition of sufficient purified fibronectin to cord plasma has been noted to increase opsonic activity against group B streptococcus.[30] Thus, impaired opsonic activity in the neonate may be secondary to impaired circulating antibody, depressed classic and alternative complement pathways, and reduced levels of fibronectin.



Neonatal sepsis treated with polymorphonuclear neutrophil leukocyte (PMN) tranfusions vs supportive care with or without intravenous immunoglobulin (IVIG).

NEUTROPHIL TRANSFUSIONS IN NEONATAL SEPSIS

Quantitative and qualitative abnormalities in neonatal myeloid bone marrow precursors and circulating PMNs have suggested the possible role of PMN transfusions as an adjuvant form of therapy in the treatment of overwhelming neonatal sepsis. To evaluate the potential role of granulocyte transfusions in this clinical setting, a randomized and prospective trial has been ongoing at our institution, Childrens Hospital of Orange County, Orange, Calif, since 1983. In the first group, described in 1987, 35 newborns were randomized to receive supportive care and leukocyte transfusions or supportive care alone.[31,32] In the second group, patients were randomized to receive supportive care and identical leukocyte transfusions and were compared with patients receiving supportive care plus intravenous immunoglobulin.[33] Infants eligible for this study were randomly selected and met the following criteria: age less than 28 days, weight greater than 800 g, and signs of overwhelming neonatal sepsis. Before randomization the infants were divided into two weight groups, 800 to 2500 g and greater than 2500 g, in an attempt to avoid having large numbers of premature infants in only one group.

Pretreatment evaluations included demographic analysis of weight, gestational age, prematurity, and postnatal age. Clinical evaluations included the following conditions: hypoxia, defined by a requirement of more than 50% forced inspired oxygen and ventilatory support; acidosis, defined by an initial pH of less than 7.2; and hypotension, defined by blood pressure of less than 55/35 mm Hg in the term infants and less than 45/25 mm Hg in the preterm infants and a requirement for blood pressure support. Laboratory evaluations included analysis of C-reactive protein; the initial hematocrit; the platelet count; the absolute granulocyte count; serum IgG, IgM, and IgA levels; and assessment of the neutrophil storage pool. Neutropenia was defined by an absolute neutrophil count (ANC) of less than 1500 cells/mm^3.

Patients were entered into the study based on the presence of at least one of the following criteria: positive blood culture, positive cerebrospinal fluid Gram's staining or culture; chest roentgenogram consistent with lobar pneumonia; or clinical features typical of necrotizing enterocolitis. If the above criteria were pending at the time of diagnosis, neonates could be entered if they had clinical deterioration with at least two major findings consistent with sepsis, including hypotension, lethargy, respiratory distress, sclerema, or thrombocytopenia. In addition, two minor criteria could be substituted for one major criteria, including maternal amnionitis, maternal fever, fetal tachycardia, or prolonged rupture of the membranes. The use of major and minor criteria allowed for a much earlier prediction of neonatal sepsis. Therefore, earlier treatment could be initiated in an attempt to reduce morbidity and mortality.

The PMN transfusions were obtained from normal adult donors by continuous-flow centrifugation leukapheresis (Cobe 2997). The donors were blood group–compatible with their neonatal recipients and screened for hepatitis, cytomegalovirus (CMV), and human immunodeficiency virus (HIV). Whenever possible, family members, especially fathers, were used. Hydroxyethyl starch was used as a sedimenting agent. Donors were given 20 mg of prednisone as a stimulant 24 hours before leukapheresis. To prevent graft-vs-host disease, each collection of PMNs was treated with 15 Gy before transfusion. The dosage of each PMN transfusion was 15 mL/kg and contained a total of 0.5 to 1×10^9 PMNs with less than 10% lymphocytes.

The first transfusion was given within the first four hours of diagnosis and then twice daily for the first two days; a single transfusion was given on the third day of illness. The first group of 35 patients was randomized to receive PMN transfusions or supportive care, including intravenous antibiotics and ventilatory and blood pressure support. The second group was randomized to the identical PMN transfusion protocol or intravenous gamma globulin infusions administered as 1000 mg/kg over four to six hours once a day for the first three days of illness. There was a total of 35

Table 2.—Comparison Studies of PMN Transfusions for Neonatal Sepsis*

Study, y	Method	Selection Criteria	Dose of PMNs	No. of Transfusions	NSP Depletion	Time Administered	Patient Survival (Control vs PMN Transfusion)
Cairo et al,[33] 1988	Continuous-flow centrifugation	Positive culture or presumed sepsis	0.75×10^9	5	4/52	4 h	Increased (10/21 vs 30/31 [48% vs 97%])
Laurent et al[34] 1981	Continuous-flow filtration	Positive culture	$0.5\text{-}1.0 \times 10^9$	2-15	. . .	Early	Increased (5/18 vs 18/20 [28% vs 90%])
Christensen et al,[35] 1982	Continuous-flow centrifugation	Positive culture + NSP	0.7×10^9	1	16/16	Early	Increased (1/9 vs 7/7 [11% vs 100%])
Baley et al,[36] 1987	Stored buffy coat	Positive culture or presumed sepsis	0.35×10^9	1-3	9/25	2 h	No change (9/13 vs 7/12 [69% vs 58%])
Wheeler et al,[37] 1987	Stored buffy coat	Positive culture + NSP	0.4×10^9	1	9/28	2.5 h	No change (2/5 vs 2/4 [40% vs 50%])

*PMNs indicates polymorphonuclear neutrophil leukocytes; NSP, neutrophil storage pool.

patients in the first randomization and 17 patients in the second randomization. There were 31 patients who received PMN transfusions and 21 patients who received supportive care alone or supportive care plus intravenous immunoglobulin (Figure).

The pretreatment demographic data disclosed no significant difference in the treatment groups when comparing initial weight, gestational age, prematurity, or postnatal age. When survival vs nonsurvival was analyzed, there was again no significant difference in any of these demographic variables. Pretreatment laboratory variables that were also found to be insignificant between the PMN transfusion and intravenous immunoglobulin–supportive groups included positivity for C-reactive protein, initial hematocrit, initial platelet count, initial ANC, ANC less than or equal to 1500/mm^3, and serum IgM and IgA levels. Differences in these same variables were also not statistically significant between survivors and nonsurvivors. Finally, pretreatment clinical conditions that were also found to be insignificantly different between the groups with and without transfusions and between survivors and nonsurvivors included hypoxemia, acidosis, and hypotension.

There were only four patients in the present study who had true neutrophil storage pool depletion as defined by less than 7% PMNs, band cells, and metamyelocytes. However, 35 of the 52 septic neonates presented with an absolute granulocyte count greater than or equal to 2500/mm^3. Tibial bone marrow aspiration proved to be a useful diagnostic tool in distinguishing true neutrophil storage pool depletion from peripheral granulocyte consumption. Only four (11%) of 35 of the neutropenic neonates had true neutrophil storage pool depletion.

The incidence of positive bacterial blood cultures or disorders often associated with neonatal sepsis was similar in both groups. Group B streptococcus was isolated from 13 of the 52 patients, including eight in the transfusion group compared with five in the supportive care and intravenous immunoglobulin group. There was a wide distribution of organisms noted in 51 of 52 neonates.

The neutrophil storage pool at the time of sepsis appeared to be an important prognostic factor in the outcome of neonatal sepsis. Although only four of 52 patients had true neutrophil storage pool depletion, there appeared to be a difference in survival when the total neutrophil storage pool was compared between the two groups. In the nonsurvivor group the mean (± SD) neutrophil storage pool (PMN + band cells + metamyelocytes) was 18% ± 5%, compared with 32% ± 3% in the survival group ($P \leq .001$). Therefore, the diagnostic use of tibial bone marrow aspirates in neonates with neutropenia and overwhelming sepsis proved to be an important tool in predicting the severity of neonatal sepsis.

The most important finding in our study was a striking difference in mortality between the two treatment groups. There was a marked improvement in survival in the group of neonates who received PMN transfusions compared with the group receiving supportive care and intravenous immunoglobulin. In the neonates receiving PMN transfusions, 30 of 31 patients survived, compared with 11 of 21 patients in the supportive care and intravenous immunoglobulin group ($P \leq .004$) (Figure). Additionally, in the second randomization comparing PMN transfusions with intravenous immunoglobulin, all of ten patients in the PMN transfusion group survived, compared with three of seven patients in the intravenous immunoglobulin group ($P \leq .05$). All deaths in this study were secondary to sepsis or septic complications. Additionally, there were no adverse effects in the PMN transfusion group, including graft-vs-host disease; fluid overload; CMV, hepatitis, or HIV infection; blood group sensitization; or pulmonary insufficiency.

Several other investigators have used PMN transfusions in an attempt to enhance the neonate's immune response to bacterial sepsis. These studies each in-

cluded small number of patients, used different methods of obtaining PMNs, utilized different transfusion protocols, and had substantially different outcomes (Table 2). Laurenti et al[34] reported the successful use of PMN transfusions in a retrospective analysis of 20 neonates with gram-negative sepsis. This study was not a randomized study and PMNs were obtained by continuous-flow filtration leukapheresis. Neonates were given anywhere from two to 15 transfusions during this treatment protocol. The improved survival rate was most striking in the subgroup of infants who weighed less than 1500 g. The mortality rate was 10% in the transfusion group vs 91% in the no transfusion group. Unfortunately, this was a retrospective study and not a controlled and randomized study, but its results did suggest the possible benefit of PMN transfusions.

Christensen et al[35] reported in a controlled randomized fashion the effect of PMN transfusions in septic neutropenic neonates with severe neutrophil storage pool depletion. Seven neonates received a single PMN transfusion that was obtained by continuous-flow centrifugation leukapheresis (cell count, 0.7×10^9/mL). There was 100% survival in this treatment group. Nine similar neutropenic, septic neonates with storage pool depletion did not receive PMNs. There was only one survivor, for a survival rate of 11%. This prospective randomized study suggested the benefit of PMN transfusion obtained by continuous-flow centrifugation and administered to septic neonates with neutrophil storage pool depletion.

Baley et al[36] reported in a randomized prospective study the use of stored buffy coat PMNs in the treatment of neonatal sepsis. The buffy coats were obtained and stored for a maximum of 24 hours before use. The total number of PMNs was almost 50% less than in previous studies (cell count, 0.35×10^9/mL). Neonates were given one to three transfusions. Nine of 25 patients had true neutrophil storage pool depletion at the time of sepsis. The buffy coat transfusions were given within two hours of diagnosis. Baley and colleagues, however, evaluated the following three separate neonatal populations: infants weighing less than 1500 g with presumed sepsis; infants weighing 1500 g or more with presumed sepsis; and infants with necrotizing enterocolitis. There were eight patients in the first group, five patients in the second group, and 12 patients in the third group, and they were merged and analyzed together (12 with buffy coat transfusions and 13 without). The age at admission in the transfusion group was 20 ± 15 days, a somewhat older patient population than in previous studies by Christensen et al,[35] Laurenti et al,[34] and Cairo et al.[32] Although the number of patients in the study by Baley and colleagues[36] was small, they found no significant difference in survival among the combined treatment groups.

Wheeler et al[37] also examined the role of stored buffy coat transfusions in the treatment of neonatal sepsis with neutrophil storage pool depletion. The dose of PMNs in the buffy coat was approximately the same as in the study by Baley et al[36] (cell count, 0.4×10^9/mL). Wheeler et al administered the buffy coat within 2½ hours of diagnosis. There was only a small number of patients in their study. There were only nine neonates with neutrophil storage pool depletion (≤7% PMN + band cells + metamyelocytes); four of them received transfusions, compared with five neonates who did not. The mortality was equal in both groups.

The present study differed in several respects from the above-mentioned studies. The present study included the largest group of randomized patients and utilized PMNs obtained by continuous-flow centrifugation leukapheresis, similar to the study by Christensen et al,[35] and avoided PMNs obtained by continuous-flow filtration or buffy coat preparations. The dose of PMN transfusions was different in each group. Our study was consistent with those by Laurenti et al[34] and Christensen et al[35] (cell count, 0.75×10^9/mL), an amount almost twice the dose used in the buffy coat transfusion studies (0.35×10^9/mL). Despite the return of the PMN counts to normal within the first 36 to 48 hours, we used a unique transfusion schedule of one PMN transfusion given every six to 12 hours for a total of five transfusions. The high percentage of positive blood cultures in our study was consistent with those in previously published studies. Finally, we also attempted to administer PMN transfusions as early as possible, averaging four hours from the time of diagnosis.

Several questions still remain to be answered regarding the future use of adult-donor PMN transfusions in the treatment of neonatal sepsis. Variables that still need to be studied include selection criteria to define which group of septic neonates require early PMN administration, the number of PMNs that need to be harvested, a method of quick and optimal collection, the frequency and intervals of PMN transfusions, and the role of plasma factors such as complement or intravenous gamma globulin that promote phagocytosis of transfused PMNs. The benefits of PMN transfusions must be weighed against reported side effects such as fluid overload from hydroxyethyl starch and high fluid content; graft-vs-host disease; CMV, HIV, and hepatitis infections; and blood group sensitization. A large multicenter study of the role of PMN transfusions vs supportive care with or without adjuvant plasma or intravenous gamma globulin therapy is warranted on the basis of the previous studies referred to during this discussion.[36-38]

ROLE OF INTRAVENOUS IMMUNOGLOBULIN

The use of immunoglobulin therapy was first studied in several septic neonatal animal models. Intravenous immunoglobulin has been shown by Harper et al[38,39] to improve the mortality rate among antibiotic-treated neonatal rats infected with either group B streptococcus or *E coli*. Additionally, the administration of intravenous immunoglobulin in infected neonatal rats may not only improve their mortality but in fact may prevent neutrophil storage pool depletion.[38] Recently, the use of monospecific or monoclonal immunoglobulin directed against specific antigenic determinants on neonatal bacterial pathogens has been examined as an adjuvant form of therapy in neonatal sepsis.[40-42] Fischer et al[40] demonstrated opsonic and protective activity and significant elevations in group B streptococcal–specific IgG in human neonates receiving 500 mg/kg of intravenous immunoglobulin. Recent phase I trials have demonstrated that intravenous immunoglobulin can be given safely to premature newborns.[43,44]

The half-life of intravenous immunoglobulin administered at a dosage of 500 to 750 mg/kg/d has varied between 8½ and 14 days in the nonseptic neonate.[43,44] It appears that circulating levels of 700 mg/dL may offer the best protection against nosocomial infections in premature newborns.[45]

Conway et al[46] recently suggested the benefit of prophylactic intramuscular immunoglobulin in premature infants. They administered 50 mg/kg of gamma globulin weekly by intramuscular injection and demonstrated 22 infected episodes in 60 neonates in the treated group, compared with episodes in 40 of 60 subjects in the untreated group. Three additional studies have evaluated the prophylactic role of intravenous immunoglobulin administered to premature newborns who are at high risk for sepsis. Sidiropoulos et al[47] treated newborns suspected of having sepsis with 500 to 1000 mg/d of intravenous immunoglobulin. In those infants weighing less than 2500 g, there was only a 9% mortality rate, compared with a 44% mortality in the control untreated group. Haque et al[48] prophylactically administered to newborns a total of 1500 g or less at a dosage of 125 mg/kg on day 1 or on days 1 and 8. Sixteen percent of the untreated control infants developed sepsis, compared with 4% in the intravenous immunoglobulin group. The most comprehensive study to date, however, was reported by Chirico et al,[49] who treated infants weighing 1500 g or less with 500 mg/kg of intravenous immunoglobulin each week for four weeks. The death rate was 16% in the intravenous immunoglobulin–treated group and 32% in the untreated control group. Results of these studies should be cautiously interpreted because of recent observations by Kim and Hong.[50] They has demonstrated that high doses of human intravenous immunoglobulin may impair the therapeutic benefit of penicillin G against experimental group B streptococcal bacteremia and meningitis in the newborn rat.

The eventual role of intravenous immunoglobulin for either prophylaxis or treatment of neonatal sepsis will be indicated by the outcome of future large-scale and multicenter randomized studies. Further studies are needed before the use of the adjuvant immunologic therapy can be recommended for premature and term neonates.

OTHER FUTURE THERAPIES: LYMPHOKINE ENHANCEMENT OF NEONATAL HOST DEFENSES

The regulation of blood cell formation is a complex biologic process involving multifactorial mechanisms. A common set of pluripotent stem cells, residing mostly in the bone marrow in adults and additionally in the liver and spleen in preterm and term neonates, gives rise to large numbers of circulating neutrophils, eosinophils, monocytes, basophils, red blood cells, platelets, and lymphocytes in the peripheral blood. Recently, it has been discovered that cell division and differentiation of these hematopoietic progenitor cells are dependent on the continuous or intermittent supply of highly specific protein factors. These growth-prompting factors act as regulators of hematopoiesis and were subsequently termed *colony-stimulating factors* (CSFs).[51-53]

Colony-stimulating factors are a family of glycoproteins with biologic specificity defined by their abilities to support proliferation and differentiation of hematopoietic cells of various lineages. The recombinant forms of these proteins have been recently purified. Granulocyte-monocyte CSF (Rh-GM-CSF) and granulocyte CSF (rh-G-CSF) have similar physiologic actions on their naturally occurring proteins. Both stimulate the proliferation of bone marrow myeloid progenitor cells, induce the release of bone marrow neutrophil storage pools, and enhance mature neutrophil effector function.[51,52] Most studies to date have examined the role of GM-CSF and G-CSF in stimulating adult neutrophil bone marrow progenitor cell proliferation, storage pool release, and enhancement of peripheral neutrophil effector function.

We have recently examined the effects of GM-CSF and G-CSF on neonatal rat myeloid kinetics, neutrophil storage pool release, and human neonatal neutrophil function. The enhancement of the neonatal neutrophil oxidative metabolism by GM-CSF is similar to its effect on adult neutrophils; GM-CSF also has been demonstrated to prime neonatal neutrophils for enhanced chemotaxis and bacterial killing.[54] Both GM-CSF and G-CSF induce peripheral neutrophilia (within two to six hours of intraperitoneal administration) in newborn rats. The neutrophil count usually returns to a normal baseline by 24 hours. These preliminary studies suggest a possible role of these lymphokines in promoting neonatal neutrophil egress and effector function. Further studies are under way to determine their effect in modulating neonatal sepsis.

Nancy Franks provided editorial assistance in the preparation of this manuscript.

References

1. Siegel J, McCracken G: Sepsis neonatorum. *N Engl J Med* 1981;304:642-647.
2. Weinstein R, McCracken G: Pathogenesis and management of neonatal sepsis and meningitis. *Curr Probl Pediatr* 1977;7:3-59.
3. Christensen RD, Rothstein G: Pre and postnatal development of granulocyte stem cells (CFUc) in the rat. *Pediatr Res* 1984;18:599-602.
4. Christensen RD, Harper TE, Rothstein G: Granulocyte-macrophage progenitor cell (CFU-GM) in term and preterm neonates. *J Pediatr* 1986;109:1047-1051.
5. Erdman SH, Christensen RD, Bradley PP, et al: Supply and release of storage neutrophils: A developmental study. *Biol Neonate* 1982;41:132-137.
6. Christensen RD, Macfarlane JL, Taylor NL, et al: Blood and marrow neutrophils during experimental group B streptococcal infection: Quantification of the stem cell, proliferative, storage and circulating pools. *Pediatr Res* 1982;16:549-553.
7. Hill HR: Biochemical, structural and functional abnormalities of polymorphonuclear leukocytes in the neonate. *Pediatr Res* 1987;22:375-382.
8. Miller M: Chemotactic function in the human neonate: Humoral and cellular aspects. *Pediatr Res* 1971;5:487-492.
9. Klein R, Fischer T, Gard S, et al: Decreased mononuclear and polymorphonuclear chemotaxis in human newborns. *Pediatrics* 1977;60:467-472.
10. Wright WC, Ank B, Stiehm E: Decreased bacterial capacity of leukocytes of stressed newborns. *Pediatrics* 1975;56:579-584.
11. Shigeoka A, Santos J, Hill H: Functional analysis of neutrophil granulocytes from healthy infected and stressed newborns. *J Pediatr* 1979;95:454-460.
12. Miller ME. Phagocyte function in the neonate: Selected aspects. *Pediatrics* 1979;64 (suppl):709-715.
13. Anderson DC, Pickering LK, Feigin RD: Leukocyte function in normal and infected neonates. *J Pediatr* 1974;85:420-426.
14. Anderson DC, Hughes BJ, Smith CW: Abnormal mobility of neonatal polymorphonuclear leukocytes. *J Clin Invest* 1981;68:863-874.
15. Miller ME: Phagocytosis in the newborn: Humoral and cellular factors. *J Pediatr* 1969;75:255-259.
16. Forman ML, Stiehm ER: Impaired opsonic activity but normal phagocytosis in low-birth

weight infants. *N Engl J Med* 1969;281:926-931.

17. Ambruso DR, Altenburger KM, Johnston RB: Defective oxidative metabolism in newborn neutrophils: Discrepancy between superoxide anion and hydroxyl radical generation. *Pediatrics* 1979;64(suppl):722-725.

18. Ambruso DR, Bentwood B, Henson PM, et al: Oxidative metabolism of cord blood neutrophils: Relationship to content and degranulation of cytoplasmic granules. *Pediatr Res* 1984;18:1148-1153.

19. Shigeoka AO, Charette RP, Wyman ML, et al: Defective oxidative metabolic responses of neutrophils from stressed neonates. *J Pediatr* 1981; 98:392-398.

20. Bruce MC, Baley JE, Medvik KA, et al: Impaired surface membrane expression of C3bi but not C3b receptors on neonatal neutrophils. *Pediatr Res* 1987;21:306-311.

21. Anderson DC, Freeman KLB, Heerdt B, et al: Abnormal stimulated adherence of neonatal granulocytes: Impaired induction of surface MAC-1 by chemotactic factors or secretagogues. *Blood* 1987;70:740-750.

22. Ballow M, Cates KL, Rowe JC, et al: Development of the immune system in very low birth weight (less than 1500 g) premature infants: Concentrations of plasma immunoglobulins and patterns of infections. *Pediatr Res* 1986;20:899-904.

23. Cates KL, Rowe JC, Ballow M: The premature infant as a compromised host. *Curr Probl Pediatr* 1983;13:1-63.

24. Baker CJ, Edwards MS, Kasper DL: Role of antibody to native type III polysacccharide of group B streptococcus in infant infection. *Pediatrics* 1981;68:544-549.

25. Bankhurst AD, Morito T, Williams RC: Studies of human cord blood and adult lymphocyte interactions with in vitro immunoglobulin production. *J Clin Invest* 1979;64:990-995.

26. Nagaoki T, Mitawaki T, Ciorbaru R, et al: Maturation of B cell differentiation ability and T cell regulatory function during child growth assessed in a *Nocardia* water-soluble mitogen-drive system. *J Immunol* 1981;126:2015-2019.

27. Anderson DC, Hughes BJ, Edwards MS, et al: Impaired chemotaxigenesis by type III group B streptococci in neonatal sera: Relationship to diminished concentration of specific anticapsular antibody and abnormalities of serum complement. *Pediatr Res* 1983;17:496-502.

28. McCracken GH Jr, Eichenwald HF: Leukocyte function and the development of opsonic and complement activity in the neonate. *AJDC* 1971;121:120-126.

29. Stossel TP, Alper CH, Rosen F: Opsonic activity in the newborn: Role of properdin. *Pediatrics* 1973;52:134-137.

30. Gerdes JS, Yoder MC, Douglas SD, et al: Decreased plasma fibronectin in neonatal sepsis. *Pediatrics* 1983;72:877-881.

31. Cairo MS, Rucker R, Bennetts GA, et al: Improved survival of newborns receiving leukocyte transfusion for sepsis. *Pediatrics* 1984;74:887-892.

32. Cairo MS, Worcester C, Rucker R, et al: Role of circulating complement and polymorphonuclear leukocyte transfusion in treatment and outcome in critically ill neonates with sepsis. *J Pediatr* 1987;110:935-941.

33. Cairo MS, Sender L, Worcester C, et al: A prospective randomized trial demonstrating the importance of bone marrow reserves and the advantage of PMN transfusion vs intravenous gammaglobulin or supportive care in neonatal sepsis: Preliminary observations and expansion of previous study population, abstracted. *Pediatr Res* 1988; 23:471A.

34. Laurenti F, Ferro R, Isacchi G, et al: Polymorphonuclear leukocyte transfusion for the treatment of sepsis in the newborn infant. *J Pediatr* 1981;98:118-122.

35. Christensen RD, Rothstein G, Anstall HB, et al: Granulocyte transfusions in neonates with bacterial infection, neutropenia, and depletion of mature marrow neutrophils. *Pediatrics* 1982; 70:1-6.

36. Baley JE, Stork EK, Warkentin PI, et al: Buffy coat transfusions in neutropenic neonates with presumed sepsis: A prospective, randomized trial. *Pediatrics* 1987;80:712-720.

37. Wheeler JG, Chauvenet AR, Johnson CA, et al: Buffy coat transfusions in neonates with sepsis and neutrophil storage pool depletion. *Pediatrics* 1987;79:422-425.

38. Harper TE, Christensen RD, Rothstein G, et al: Effect of intravenous immunoglobulin G on neutrophil kinetics during experimental group B streptococcal infection in neonatal rats. *Rev Infect Dis* 1986;8(suppl):S401-S408.

39. Harper TE, Christensen RD, Rothstein G: The effect of administration of IgG to newborn rats with *E coli* sepsis and meningitis. *Pediatr Res* 1987;22:455-460.

40. Fischer GW, Weisman LB, Hemming VG, et al: Intravenous immunoglobulin in neonatal group B streptococcal disease. *Am J Med* 1984;76(suppl):117-123.

41. Bortolussi R, Fischer GW: Opsonic and protective activity of immunoglobulin, modified immunoglobulin, and serum against neonatal *Escherichia coli* K1 infection. *Pediatr Res* 1986;20:175-178.

42. Givner LB: Human IgG hyperimmune for type III group B streptococcus (III-GBS): Efficacy in newborn rats, abstracted. *Pediatr Res* 1988;23:473A.

43. Ruderman JW, Gill RC, Pomerance JJ, et al: Use of IVIG in hypogammaglobulinemia of prematurity, abstracted. *Clin Res* 1988;36:234A.

44. Christensen RD, Hardimen T, Thornton J, et al: A randomized double blind placebo-controlled trial of IVIG administration in premature infants, abstracted. *Clin Res* 1988;36:471A.

45. Clapp DW, Baley JE, Kliegman RM, et al: Randomized trial of IVIG to prevent nosocomial infections in preterm infants: Preliminary data, abstracted. *Pediatr Res* 1988;23:471A.

46. Conway SP, Gillies DRN, Doherty A: Neonatal infection in premature infants and use of human immunoglobulin. *Arch Dis Child* 1987;62:1252-1256.

47. Sidiropoulos D, Boehme U, Muralt GV, et al: Immunoglobulin supplementation in prevention or treatment of neonatal sepsis. *Pediatr Infect Dis* 1986;5:S185-S188.

48. Haque KN, Zaidi MN, Haque SK, et al: Intravenous immunoglobulin for prevention of sepsis in preterm and low birth weight infants. *Pediatr Infect Dis* 1986;5:622-625.

49. Chirico G, Rondini G, Plebani A, et al: Intravenous gamma globulin therapy for prophylaxis of infection in high-risk neonates. *J Pediatr* 1987; 110:437-442.

50. Kim KS, Hong JK: High dose of human intravenous immunoglobulin (IVIG) may impair therapeutic benefit of penicillin G (P) against experimental group B streptococcal bacteremia and meningitis, abstracted. *Pediatr Res* 1987; 417A:1459.

51. Clark SC, Kamen R: The human hematopoietic colony-stimulating factors. *Science* 1987; 236:1229-1237.

52. Sieff CA: Hematopoietic growth factors. *J Clin Invest* 1987;79:1549.

53. Moore MA: In vivo and in vitro action of hematopoietic colony stimulating factors. *Proc Am Assoc Cancer Res* 1987;28:466-469.

54. Cairo MS, VandeVen C, Toy C, et al: Lymphokines: GM-CSF and G-CSF enhancement of neonatal myeloid kinetics and PMN functional activation. *Rev Infect Dis*, in press.

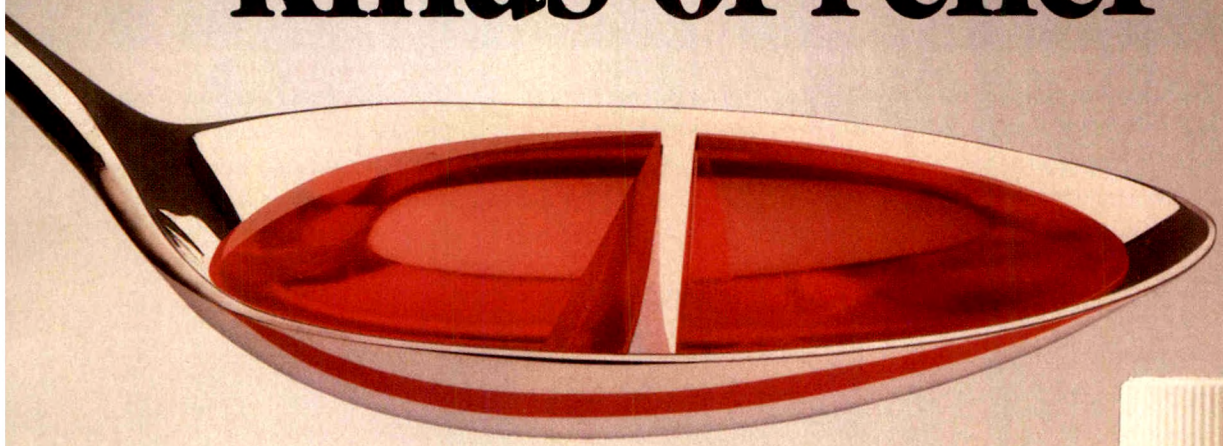
In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Surgical Pathology Computer Systems Have Come of Age

Raymond D. Aller, MD (*Arch Pathol Lab Med* 1988;112:1186-1187)

Think of it as two kinds of relief



One for colds

Like all Triaminic® products, Triaminicol® starts with a proven decongestant to reduce nasal and sinus congestion.

In addition, Triaminicol contains an effective antihistamine to dry runny noses and itchy, watery eyes.

And one for coughs

To stop coughs cold, Triaminicol contains dextromethorphan, a centrally acting antitussive that is non-narcotic, but equally as effective as codeine.[1-3†]

And Triaminicol does it all *without analgesics or alcohol.*

PEDIATRICIAN #1 RECOMMENDED

Triaminicol®
MULTI-SYMPTOM COLD SYRUP

†Except in severe cough

For the cold with a cough

REFERENCES

1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986; pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharm Times* 1985;51(1):80-90.

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

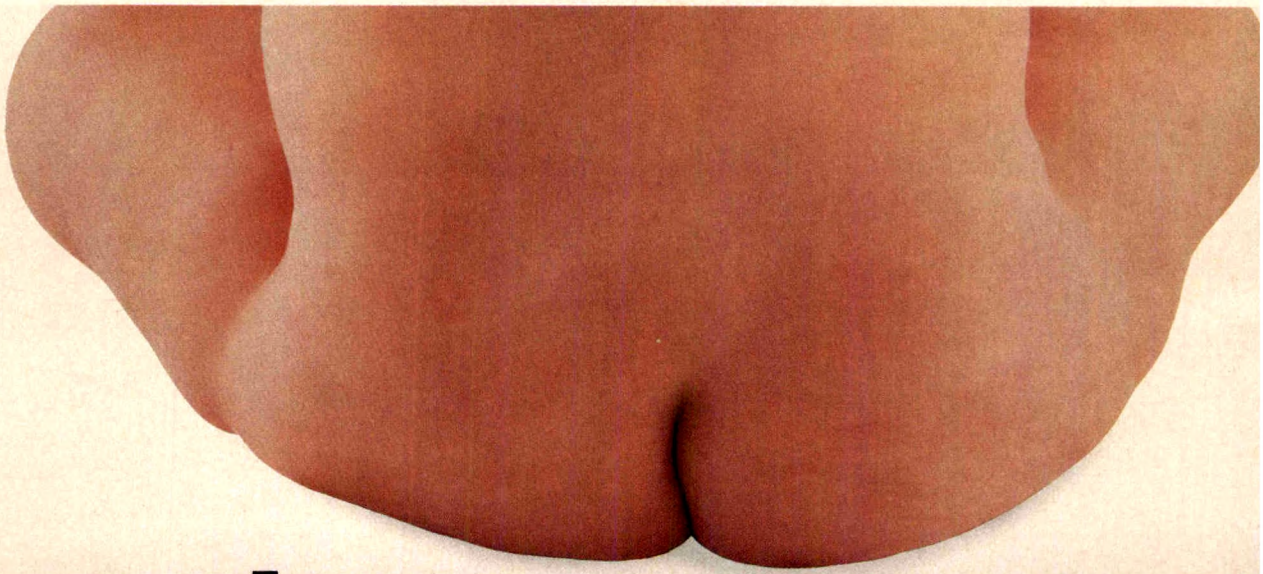
© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

EAT, DRINK, AND BE BURIED.

Go ahead. Live it up while you can. Eat anything and everything you want, from those processed meats to fatty dairy products to that extra measure of salt. But do it soon. Because poor eating habits can lead to high blood cholesterol, which can result in clogged arteries, a damaged heart, and an early death. The American Heart Association urges you to eat sensibly. Avoid food high in fat, salt and cholesterol. Avoid eating too much. It could keep you from an early grave and let you live it up a little longer.

American Heart Association WE'RE FIGHTING FOR YOUR LIFE

This space provided as a public service.



THERE'S NO REASON TO TI

CALIFORNIA

The Permanente Medical Group, Inc., Stockton, California, is currently recruiting for BC/BE pediatricians. There are presently seven pediatricians in the department and we are rapidly growing.

Send inquiries to:
Chief of Pediatrics
The Permanente Medical Group, Inc.
1305 Tommydon Street
Stockton, California 95210

Southeast USA
(Academic Pediatrician Wanted)

Alabama Board Certified or Board Eligible Academic Pediatrician, Assistant Professor. Teaching medical students and family practice residents, direct patient care and clinical research interests are required.

Direct inquiries with C.V. to:
David C. Hefelfinger, M.D.
Dept. of Pediatrics
700 University Blvd.
East, Tuscaloosa,
Alabama 35401
(205)348-1304

Equal Opportunity Affirmative Action Employer.

STREP TEST™
SHEEP BLOOD AGAR PLATES
LABORATORY CULTURE MATERIALS

- BACITRACIN DISKS
- URI-DIP®
  URINE CULTURE MATERIALS
- DELUXE INCUBATORS
- DISPENSERS
- INNOCULATING LOOPS
- SWABS

AVAILABLE FROM:

UNIVERSAL BIOLOGICAL LABS
DIAGNOSTIC DIVISION OF:
NATIONAL BIOLOGICAL CORPORATION

1532 ENTERPRISE PARKWAY
TWINSBURG, OHIO 44087
(216) 425-8180
OUTSIDE OHIO: 1-800-338-5045
IN OHIO: 1-800-227-6294

ORDER TODAY
FOR IMMEDIATE DELIVERY

AT A CHILD LIKE AN ADULT.

Diaper rash is often treated with the same medications used to treat athlete's foot. The safety and efficacy of these more potent steroid/antifungal combinations, such as Lotrisone® (clotrimazole, USP and betamethasone dipropionate, USP),† have not been established in children under the age of 12.[1] Mycolog®-II, however, has been proven clinically effective even in children as young as 2 months old.[2] Mycolog-II. It's the right way to treat a child.

Please see next page for Brief Summary of Prescribing Information.

References: 1. Lotrisone full Prescribing Information. 2. Mycolog-II full Prescribing Information.

The combination steroid/antifungal specifically indicated for cutaneous candidiasis.

MYCOLOG®-II D.A.W.*
(nystatin and triamcinolone acetonide cream, USP)

*Dispense as written.
†Lotrisone is a registered trademark of Schering Corporation, USA.

SQUIBB DERM
Innovation in topical delivery

MYCOLOG®-II

Nystatin and Triamcinolone Acetonide Cream USP and Ointment

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION: MYCOLOG-II Cream and Ointment (Nystatin and Triamcinolone Acetonide Cream USP and Ointment) for dermatologic use provide 100,000 units of the antifungal agent nystatin and 1.0 mg of the synthetic corticosteroid triamcinolone acetonide per gram.

CONTRAINDICATIONS: This preparation is contraindicated in those patients with a history of hypersensitivity to any of its components.

PRECAUTIONS: General—Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

If irritation or hypersensitivity develops with the combination nystatin and triamcinolone acetonide, treatment should be discontinued and appropriate therapy instituted.

Laboratory Tests—If there is a lack of therapeutic response, appropriate microbiological studies (e.g., KOH smears and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens, before instituting another course of therapy.

A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating hypothalamic-pituitary-adrenal (HPA) axis suppression due to corticosteroid.

Carcinogenesis, Mutagenesis, and Impairment of Fertility—Long-term animal studies have not been performed to evaluate carcinogenic or mutagenic potential, or possible impairment of fertility in males or females.

Pregnancy Category C—There are no teratogenic studies with combined nystatin and triamcinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Therefore, any topical corticosteroid preparation should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Topical preparations containing corticosteroids should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers—It is not known whether any component of this preparation is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised during use of this preparation by a nursing woman.

Pediatric Use—In clinical studies of a limited number of pediatric patients ranging in age from two months through 12 years, nystatin-triamcinolone cream formulation cleared or significantly ameliorated the disease state in most patients.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS: A single case (approximately one percent of patients studied) of acneform eruption occurred with use of combined nystatin and triamcinolone acetonide in clinical studies.

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even during prolonged use. Rarely, irritation may occur.

The following local adverse reactions are reported infrequently with topical corticosteroids (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermitiitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS, General); however, acute overdosage and serious adverse effects with dermatologic use are unlikely.

DOSAGE AND ADMINISTRATION: The use of these preparations should be discontinued if symptoms persist after 25 days of therapy (see PRECAUTIONS, Laboratory Tests). MYCOLOG-II Cream and Ointment should *not* be used with occlusive dressings.

HOW SUPPLIED: MYCOLOG-II Cream (Nystatin and Triamcinolone Acetonide Cream USP) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

MYCOLOG-II Ointment (Nystatin and Triamcinolone Acetonide Ointment) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

Storage—Store at room temperature, avoid freezing cream.

(J4-019A/ J4-024)

Innovation in topical delivery

SQUIBB DERM

CHANGE

NATIONAL INITIATIVE FOR SCIENCE AND TECHNOLOGY EDUCATION

STRATEGIES FOR

In our world today, we are experiencing fast-paced growth and global advancement in the sciences and technology. At the same time, *science literacy* is declining in America. Many adults and children don't understand the rudiments of science and its integral role in our lives. This trend toward declining science literacy will undoubtedly have important repercussions in the future. Our economic stability, national security and personal health and well-being all depend upon continued progress in the sciences.

It's a serious matter, and something must be done now to reverse the accelerating trend toward science illiteracy.

How do we educate our populace about science?

Finding workable answers to this question is the goal of the *National Initiative for Science and Technology Education.* Spearheaded by the American Medical Association, the National Initiative for Science and Technology Education has already galvanized the interest of more than 250 representatives from the fields of science, education, government, industry, the media and the military. Together they are offering to unite their efforts and take action toward improving science literacy in America. To this end, *Strategies for Change,* a national conference, will be held March 13-15, 1989 in Washington, DC. The conference will serve as the initiative's genesis for formulating a national agenda and specific strategies to accomplish the task.

Let your voice be heard.

Only through mutual dedication and effort from a wide range of professionals can we orchestrate change. Please join in this historic initiative to secure our future–and our children's future.

To register, or for additional information, please call 1-800-621-8335. In Illinois call collect 312-645-4987.

(In order to defray costs, a registration fee will be charged. The fee for registration before February 1, 1989 will be $175; thereafter, $225 will be charged.)

The *National Initiative on Science and Technology Education* is being spearheaded by the American Medical Association and planned in unison with the following groups:

American Association for the Advancement of Science
American Dental Association
Commission on Professionals in Science and Technology
Council of Scientific Society Presidents
Federation of American Societies for Experimental Biology
Institute of Electrical and Electronics Engineers
Museum of Science and Industry of Chicago

Chlamydia and the Adolescent Girl

The Enzyme Immunoassay as a Screening Tool

Karen Soren, MD, Earnestine Willis, MD, MPH

• To evaluate the enzyme immunoassay for *Chlamydia* detection in a population of sexually active urban adolescent girls, 100 endocervical screens using both immunoassay and tissue cell culture were performed. Prevalence of *Chlamydia trachomatis* was 35%, with more than two thirds of infected adolescents being asymptomatic. When compared with cell culture, the immunoassay was determined to have a sensitivity of 74%, a specificity of 98%, and positive and negative predictive values of 96% and 88%, respectively. Adolescents with false-negative immunoassay test results were more likely to lack evidence of cervical inflammation on examination and have lower-titer infections than their peers with positive results. When the immunoassay was matched against culture for test of cure after therapy, a 10% false-positive rate was found. We conclude that the immunoassay is a useful screening technique for detection of *Chlamydia* in high-risk adolescent populations; however, its limitations with respect to decreased sensitivity in asymptomatic girls and poor positive predictive value in the context of tests of cure must be appreciated.

(*AJDC* 1989;143:51-54)

As the prevalence of *Chlamydia trachomatis* infection among sexually active adolescents skyrockets, and federal and state funding for family planning and sexually transmitted disease screening dwindles, providers of adolescent health care to inner-city youth are faced with a dilemma. Should all high-risk adolescent girls be routinely screened for *Chlamydia* cervicitis, and if so, by which method and at what cost? In settings where resources are limited, should tests of cure after completion of therapy be performed, as is commonly done after treatment for *Neisseria gonorrhoeae*, and if so, again, by which method?

The traditional method for detection of *C trachomatis* has been direct cell culture, often a costly and time-consuming process, best performed by laboratories with a great deal of experience with *Chlamydia* isolation. More recently, newer rapid diagnostic techniques have become available; these include the fluorescein-conjugated monoclonal antibody direct specimen test (MicroTrak, Syva Co, Palo Alto, Calif) and the enzyme immunoassay (Chlamydiazyme, Abbott Laboratories, North Chicago, Ill). Health care facilities with limited resources and financial restraints often rely on these less expensive screening techniques for use in certain high-risk populations.

We chose to evaluate the Chlamydiazyme immunoassay within a population of sexually active urban adolescent girls attending a general adolescent health center to determine its usefulness for purposes of routine screening as well as for obtaining tests of cure after therapy. We also undertook to correlate the results of the immunoassay with the presence or absence of clinical findings on examination to assess the reliability of this screening test for use in asymptomatic adolescent girls.

PATIENTS AND METHODS

Patient Population

The study population consisted of adolescent girls who presented to an adolescent clinic associated with the University of Chicago Medical Center between November 1986 and April 1987. One hundred consecutive sexually active adolescent girls who underwent pelvic examinations for any reason were recruited into the study. Exclusion criteria were current menstruation and use of any antibiotic within 30 days prior to the screening procedure. The project was approved by the University of Chicago Clinical Investigation Committee, and signed informed consent was obtained from all participants.

Prior to screening, demographic data, gynecologic and sexual histories, and genital tract symptom reviews were collected from all patients using a standardized questionnaire. Each patient was asked prior to examination if she thought that she had a vaginal or cervical infection, and the response was recorded. To standardize data and specimen collection, all adolescents were examined by one experienced physician. Immediately after physical examination was performed, this physician recorded the presence or absence of mucopurulent cervical discharge, cervical erythema, and cervical friability. No attempt was made in this study to distinguish between cervical erythema and ectopy, as this would have required more sophisticated methodology than was available in this clinical setting. For the purposes of this study, any adolescent whose examination results were positive for at least two of the three aforementioned cervical findings was judged to have results consistent with cervicitis.

Patients with positive *Chlamydia* cultures were treated according to standard protocol,[1] and antibiotics were dispensed to facilitate compliance. Infected adolescents were requested to return for tests of cure at one to three weeks after the end of therapy. At this second visit, cell culture and immunoassay specimens were collected.

Specimen Collection

With a calcium alginate swab, a specimen from the endocervix was collected and placed into transport medium containing fetal calf serum, gentamicin, amphotericin B, and vancomycin. The sample was stored at 4°C for less than 24 hours prior to cell culture. Also at this time, a Chlamydiazyme swabbing of the endocervix was performed using a

Accepted for publication April 16, 1988.

From the Department of Pediatrics, University of Chicago Pritzker School of Medicine, Wyler Children's Hospital, and the Woodlawn Maternal and Child Health Center, Chicago.

Presented in part before the Ambulatory Pediatrics Association, Washington, DC, May 3, 1988.

Reprint requests to Department of Adolescent Medicine, St Luke's/Roosevelt Hospital Center, 428 W 59th St, Room H212, New York, NY 10019 (Dr Soren).

cotton-tipped, plastic-shaft swab. This swab was inserted into a sexually transmitted disease transport tube, containing Specimen Storage Reagent, provided as part of the Chlamydiazyme kit, and stored at 4°C for less than four days until immunoassay. To control for possible detection bias related to collection order, the specimen that was collected first for each of the two *Chlamydia* tests was assigned according to the last digit of the patient's medical record number.

Laboratory Methods

Specimens for culture of *Chlamydia* were inoculated onto duplicate cyclohexamide-treated McCoy cell coverglass monolayers by centrifugation, followed by incubation at 35°C to 36°C for 48 hours. One coverslip was then stained with fluorescein-conjugated monoclonal antibodies (Syva MicroTrak Culture Confirmation Test) and examined under a fluorescence microscope for the presence of inclusion bodies. For specimens negative on this examination, the companion coverglass was incubated for an additional 24 hours, then harvested and passed to new McCoy cells. The coverglasses from this second passage were examined after 72 hours for the presence of inclusion bodies.

Specimens for Chlamydiazyme immunoassay were processed as outlined in the Chlamydiazyme test manual.[2] Absorbance of the specimens was determined using a spectrophotometer (Quantum II, Abbott Laboratories) at 492 nm, and cutoff values for positivity as recommended by Abbott Laboratories were used. All Chlamydiazyme samples were processed in weekly batches.

Statistical Analysis

Relationships were analyzed using χ^2 (with the Yates' continuity correction factor for all 2×2 tables) and Student's t tests. When the subgroup of patients (n = 35) with positive cultures were analyzed with respect to screening test results, the two-tailed Fisher's exact test was used when any cell in any table had an expected frequency of less than five.[3] The Wilcoxon's rank sum test was used to determine significance of relationships between cell culture titers. Statistical significance was defined as $P \leq .05$.

RESULTS

One hundred screens for *Chlamydia* were carried out on 98 adolescent girls (two patients returned during the study period for repeated pelvic examinations and fulfilled study admission criteria a second time). All adolescents who were eligible consented to participate in the study. The patients ranged in age from 14 to 19 years with a mean age of 16.7 years. All were black, reflecting the general population of this health center. The participants had been sexually active prior to screening for a mean of 22.2 months (range, one to 84 months). One third of the patients had a history of some sexually transmitted disease in the past. Fifty-eight percent of the visits were for general health care or physician-requested rechecks, and were not patient-initiated or problem-oriented. Only 15% of the visits were prompted by the presence of a vaginal discharge or recent suspected contact with a sexually transmitted disease; the rest were for miscellaneous complaints.

Table 1.—Relationship Between Symptoms and Signs of Genital Tract Infection and Endocervical Infection With *Chlamydia trachomatis*

Symptom or Sign	*Chlamydia trachomatis*, No. (%)	
	Positive (n = 35)	Negative (n = 65)
Abdominal pain	8 (23)	15 (23)
Vaginal discharge	16 (46)	35 (54)
Itching	8 (23)	17 (26)
Dysuria	8 (23)	6 (9)
Urinary frequency	5 (14)	11 (17)
Urinary urgency	4 (11)	8 (12)
Dyspareunia	6 (17)	12 (19)
Bleeding after intercourse	2 (6)	6 (9)
Abnormal vaginal bleeding	3 (9)	5 (8)
Mucopurulent cervical discharge	16 (46)	18 (28)
Cervical erythema	18 (51)	14 (22)*
Cervical friability	16 (46)	27 (42)

*$P < .005$.

The prevalence of *Chlamydia* endocervical infection in this population, as defined by tissue cell culture detection, was 35%. Three of these 35 specimens were positive by second-pass subculture only.

Relationships between *Chlamydia* endocervical infection and symptoms and signs of genital tract infection are described in Table 1. None of the symptoms elicited served to help predict the presence of *Chlamydia*. In fact, only 11 (31%) of the 35 *Chlamydia* culture–positive patients considered themselves symptomatic of a genital tract infection prior to screening. The only objective finding that was statistically significantly associated with *Chlamydia* infection was the presence of cervical erythema ($P < .005$).

When the three clinical indicators of cervical inflammation (mucopurulent cervical discharge, cervical erythema, and cervical friability) were used, and the physician based judgment of probable *Chlamydia* cervicitis on the presence of at least two of these three signs, only 17 (49%) of the 35 infected with *Chlamydia* were correctly identified. In contrast, 17 (26%) of the 65 patients who were *Chlamydia*-negative had evidence of cervical inflammation, as defined above, on examination. Only six (17%) of the *Chlamydia*-positive group considered themselves symptomatic *and* had evidence on physical examination of cervicitis, whereas 13 (37%) of the adolescents infected with *Chlamydia* had *neither* symptoms nor signs typical of cervicitis.

The Chlamydiazyme immunoassay detected 26 of the 35 patients infected with *Chlamydia* (sensitivity, 0.74 ± 0.16; 95% confidence interval). One patient tested positive by Chlamydiazyme and negative by cell culture. Using the highly sensitive two-pass cell culture system as the standard for *Chlamydia* identification, the sensitivity of the Chlamydiazyme test was 74%, the specificity 98%, the positive predictive value 96%, and the negative predictive value 88%.

The 35 adolescents with culture-proven *Chlamydia* infections were then analyzed with respect to the outcome of the Chlamydiazyme rapid diagnostic screening test (Table 2) to determine if those nine patients with false-negative Chlamydiazyme test results differed in

Table 2.—Analysis of All Patients With Culture-Proven *Chlamydia trachomatis* Infection With Respect to Chlamydiazyme Test Results

	Culture-Positive/ Chlamydiazyme-Positive (n=26)	Culture-Positive/ Chlamydiazyme-Negative (n=9)	P*
Test order (Chlamydiazyme first), No. (%)	14 (54)	6 (67)	.700
Indicators of cervical inflammation, No. (%)			
Mucopurulent cervical discharge	15 (58)	1 (11)	.022
Cervical erythema	16 (62)	2 (22)	.060
Cervical friability	14 (54)	2 (22)	.135
Patients with cervicitis (ie, having two or more of the three indicators of cervical inflammation listed above), No. (%)	16 (62)	1 (11)	.018

*Fisher's exact test was used to assess probability.

any significant way from the 26 with true-positive results. No significant differences between the two groups were found by test order or presence of symptoms of lower genital tract infection. However, the 26 patients whose infections *were* detected by the immunoassay were more likely to have a mucopurulent discharge ($P=.022$) and to have been judged to have cervicitis by the physician at the time of examination, ie, to exhibit two or more signs of cervical inflammation ($P=.018$), than were those nine whose Chlamydiazyme tests yielded false-negative results. There was also a tendency for the immunoassay-positive group to have more cervical erythema and friability than their immunoassay-negative counterparts; however, because of small sample size, this did not achieve statistical significance.

Also of interest is the observation that all nine patients with false-negative Chlamydiazyme test results had cultures positive only at low titers with low inclusion body counts (fewer than 120 inclusion bodies per coverglass). The titers of specimens testing positive by immunoassay were significantly higher ($P=.001$) than those of specimens testing negative. Included in the group of patients with false-negative immunoassay test results were all three patients whose *Chlamydia* infections were identified only by second-pass subculture (very low titer).

Twenty-nine of the 35 patients with *Chlamydia* cervicitis returned for tests of cure. Twenty-four had negative results on both cell culture and Chlamydiazyme, indicating cure. Two patients had positive results on both tests, indicating treatment failure (incidentally, both of these patients had been treated with erythromycin, and compliance had been admittedly poor). The other three patients had specimens that yielded negative cultures for *Chlamydia*, but tested weakly positive by immunoassay (had spectrophotometric values close to the cutoff points used). Hence, there was a 10% (3/29) false-positive rate when using Chlamydiazyme for test of cure, and, in this context, an overall sensitivity of 100%, specificity of 89%, positive predictive value of 40%, and negative predictive value of 100% for the immunoassay. Tests were collected between six and 119 days after the end of therapy, with a mean number of days in the 26 concordant samples of 27, and a mean number of days in the three discordant samples of nine. The difference between the two sets was found to only approach statistical significance ($P=.073$ by Wilcoxon's rank sum test), perhaps due to the small sample size.

COMMENT

The prevalence of chlamydial endocervical infection among sexually active adolescent girls found in this study (35%) was somewhat higher than anticipated, but consistent with results of similar studies of urban sexually active adolescents from other areas of the country.[4-7] The majority of infected patients in our study lacked clinical signs of cervical inflammation, and most considered themselves asymptomatic, reinforcing the data obtained by others[5,6,8] that note a high rate of asymptomatic chlamydial endocervical carriage.

The enzyme immunoassay for *Chlamydia* detection has been previously evaluated by several other authors, although most of those screening trials took place among adults who presented to family planning or sexually transmitted disease clinics. In a study of 514 adult women, Amortegui and Meyer[9] reported the sensitivity and specificity of the Chlamydiazyme immunoassay to be 82% and 98%, respectively, when compared with two-pass cell culture isolation, and Jones et al[10] obtained similar results in a study of 201 adult men and women. Chernesky et al[11] included 238 women under age 20 years in their trial, and reported the overall sensitivity and specificity of the immunoassay to be 89% and 97%, respectively. In the latter study, the data were analyzed with respect to clinical findings, and it was concluded that there was better correlation between test results and cell culture than between test results and clinical findings.

Our screening trial was admittedly much smaller, but it examined only adolescents, the majority of whom were without symptoms. We found the sensitivity of the immunoassay to be somewhat lower, at 74%. This may in part be attributable to a better gold standard, ie, a highly sensitive two-pass cell culture system implemented by a university microbiology laboratory with a great deal of experience with *Chlamydia* detection, and in part to the inclusion of a greater percentage of adolescents with low-titer, asymptomatic *Chlamydia* infections. Because of our small sample size, however, a larger screening evaluation is necessary to confirm our findings.

An analysis of the nine patients with false-negative Chlamydiazyme test results raises several interesting points. One third had cell culture specimens positive for *C trachomatis* only on second-pass subculturing; the remainder had relatively low-titer *Chlamydia* culture isolates, and almost all had normal-appearing cervices on physical examination. The data suggest that the

enzyme immunoassay may require a critical concentration of antigen to test positive, and that there may exist a population of so-called carriers, colonized with low counts of *C trachomatis*, who may escape detection by immunoassay; or perhaps those patients with false-negative Chlamydiazyme test results were screened too early in the course of their infections to be detected by immunoassay, and would have tested positive had they been rescreened several months later. The natural history of untreated cervical *Chlamydia* infections has not been well defined, but there are data to suggest that few, if any, women have spontaneous cures.[12] Also, evidence exists that subclinical infection with *C trachomatis* is related to subacute pelvic inflammatory disease, tubal scarring, and infertility.[13] Further work is needed to determine the significance of low-grade infections with *Chlamydia*, and the potential morbidity of missing these infections by using the less sensitive rapid diagnostic screening methods.

Our study also attempted to determine whether the enzyme immunoassay was a reliable method for obtaining tests of cure after completion of therapy. The specificity of the immunoassay in this context was only 89%, and the positive predictive value 40%, due to the relatively high number of false-positive results in this small sample. Admittedly, all these false-positive results were considered "weak," with spectrophotometric values close to the cutoff point. One can speculate that the discordance may have been secondary to the presence of nonviable organisms or dead antigen within the cervical secretions, as the rate of false-positive results in the test-of-cure setting was higher than the rate observed on initial screening. We were unable to demonstrate a statistically significant relationship between the number of days after therapy that the samples for test of cure were collected and concordance with culture results. However, it is possible that with a larger sample size, such a relationship may become apparent. In settings where resources are scarce, performing tests of cure is often an unaffordable luxury; nonetheless, if the immunoassay is to be used in this context, its limitations must be appreciated.

We conclude that health care facilities servicing adolescents should attempt to screen for the ubiquitous *Chlamydia* organism, and not rely on clinical data alone for its detection. In settings where cell culture is either unavailable or unaffordable, a rapid diagnostic screening test may have to suffice. If the enzyme immunoassay is to be used, its results must be interpreted with caution, as both its sensitivity on initial screening of generally asymptomatic adolescent girls, and its positive predictive value when used to determine if cure has been achieved after therapy, appear to be limited.

This study was supported by grants from the University of Chicago Children's Research Fund and Abbott Laboratories.

We thank Kolavennu Krishnaiah, PhD, for laboratory assistance; Sharron Riley for her help with manuscript preparation; and the faculty and staff of the Michigan State Primary Care Faculty Development Fellowship Program (East Lansing), especially John Pascoe, MD, MPH, and Lynn Snellman, MA, for their invaluable help with study design and analysis.

References

1. Treatment of sexually transmitted diseases. *Med Lett* 1986;28:23-27.
2. Abbott Laboratories, Diagnostics Division: *Chlamydiazyme Diagnostic Kit*. North Chicago, Ill, Abbott Laboratories, December, 1985.
3. Sanders GW, Cochran WG: *Statistical Methods*, ed 7. Ames, Iowa, Iowa State University Press, 1980.
4. Jaffe LR, Siqueira LM, Diamond SB, et al: *Chlamydia trachomatis* detection in adolescents: A comparison of direct specimen and tissue culture methods. *J Adolesc Health Care* 1986;7:401-404.
5. Saltz GR, Linnemann CC, Brookman RR, et al: *Chlamydia trachomatis* cervical infections in female adolescents. *J Pediatr* 1981;98:981-985.
6. Shafer MA, Beck A, Balin B, et al: *Chlamydia trachomatis*: Important relationship to race, contraception, lower genital tract infection, and Papanicolaou smear. *J Pediatr* 1984;104:141-146.
7. Chacko MR, Lovchik JC: *Chlamydia trachomatis* infection in sexually active adolescents: Prevalence and risk factors. *Pediatrics* 1984; 73:836-840.
8. Fisher M, Swenson PD, Risucci D, et al: *Chlamydia trachomatis* in suburban adolescents. *J Pediatr* 1987;111:617-620.
9. Amortegui AJ, Meyer MP: Enzyme immunoassay for detection of *Chlamydia trachomatis* from the cervix. *Obstet Gynecol* 1985;65:523-526.
10. Jones MF, Smith TF, Houglum AJ, et al: Detection of *Chlamydia trachomatis* in genital specimens by the Chlamydiazyme test. *J Clin Microbiol* 1984;20:465-467.
11. Chernesky MA, Mahoney JB, Castriciano S, et al: Detection of *Chlamydia trachomatis* antigens by enzymes immunoassay and immunofluorescence in genital specimens from symptomatic and asymptomatic men and women. *J Infect Dis* 1986;154: 141-148.
12. McCormack WM, Alpert S, McComb DE, et al: Fifteen month follow-up study of women infected with *Chlamydia trachomatis*. *N Engl J Med* 1979;300:123-125.
13. Moore DE, Foy HM, Daling JR, et al: Increased frequency of serum antibodies to *Chlamydia trachomatis* in infertility due to distal tubal disease. *Lancet* 1982:2:574-577.

In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY

Ethical Use of Yellow Pages Listings by Physicians

Steven M. Denenberg, MD, Howard W. Smith, MD, DMD (*Arch Otolaryngol Head Neck Surg* 1988;114:1392-1394)

Psychosocial Determinants of Compliance in Adolescents With Iron Deficiency

Barbara A. Cromer, MD; Karl Steinberg, MD; Lynne Gardner, RD, MPH; David Thornton, PhD; Barry Shannon, PhD

• The relationship between selected psychosocial variables and compliance was studied in 71 adolescents prescribed medication for iron deficiency. The mean compliance rate in the study group was 67%. Home pill counts were highly correlated with the other methods of measuring compliance, ie, change in serum ferritin level and urinary assay for tracer riboflavin. Statistically significant predictors of compliance included adverse side effects, initial estimate by the adolescent as to his probable level of compliance, and frequency of family reminders to take the medication. There was no significant correlation between self-esteem, locus of control, or most variables of the Health Belief Model and the level of patient compliance. Our findings suggest that home pill counts are an accurate method of assessing compliance and that instituting family reminders may be helpful in those adolescents who are potentially noncompliant.

(*AJDC* 1989;143:55-58)

Despite the proliferation during the past two decades of research on compliance, no consistent psychosocial profile of the compliant adolescent has emerged.[1] Conflicting results may relate to differences in the underlying health status of the study populations rather than to variations in the psychological profile. In an effort to avoid the confounding effects of disabling chronic disease, we decided to design a study of adherence in healthy adolescents with an asymptomatic medical condition, ie, iron deficiency as defined by low serum ferritin levels. The psychosocial factors that were assessed regarding their relationship with compliant behavior included self-esteem, locus of control, and personal health beliefs derived from the Health Belief Model.

Accepted for publication Sept 2, 1988.

From the Departments of Pediatrics (Drs Cromer and Steinberg and Ms Gardner) and Laboratory Medicine (Drs Thornton and Shannon), Ohio State University, Columbus.

Read before the National Meeting of the Society for Behavioral Pediatrics, Anaheim, Calif, April 26, 1987.

Reprint requests to Department of Adolescent Medicine, Children's Hospital, 700 Children's Dr, Columbus, OH 43205 (Dr Cromer).

SUBJECTS AND METHODS

Population

All adolescents presenting as new patients to the Teenage Clinic at Children's Hospital of Columbus (Ohio) were evaluated for study eligibility. Prerequisites for study enrollment included telephone ownership and residency within a 30-minute drive (to facilitate home follow-up), as well as no current use of vitamins. Those adolescents who were enrolled in the study (along with a parent) gave informed consent according to the guidelines established by the Human Subjects Research Committee of Children's Hospital. To avoid possible confounding effects of subjects' knowledge regarding the study's primary intent, study enrollees were informed that the purpose of the project was to examine iron deficiency and its treatment in teenagers.

Of 394 eligible adolescents, 343 (87%) consented to the study protocol and underwent venipuncture for measurement of serum ferritin levels (Figure). There was no significant difference between the study enrollees (initial screening group) and those refusing study participation on selected demographic variables. Of the 343 adolescents in the initial screening, 87 (26%) had evidence of iron deficiency as indicated by low serum ferritin levels. With an attrition rate of 16 (18%) over the study period, 71 adolescents constituted the final study group.

Twenty-three members (32%) of the final study group were male and 31 (44%) of the group were white. The mean age of the study group was 15.0 years with a range of 11.5 to 18.0 years. Hollingshead scores were wide ranging (11 to 61), but were skewed toward lower socioeconomic status, with a mean of 27. These data reflect the demographic distribution of the clinic's patients in general and thus do not reflect a genuine difference in prevalence rates of iron deficiency.

Study Procedure

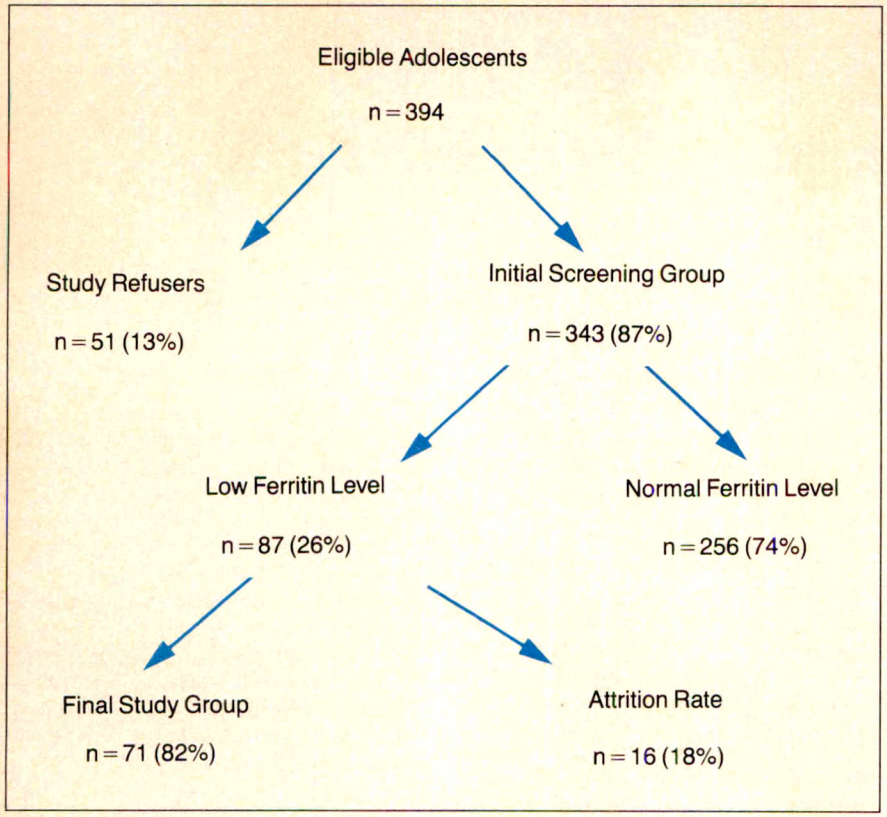
Each member of the study group was notified by telephone regarding his iron-deficiency status, and a home visit was scheduled by a member of the research staff. During this home visit the adolescent was given the iron medication in the form a multivitamin preparation, with each tablet containing 100 mg of ferrous sulfate (Stuartinic); the adolescent was instructed to take one tablet each morning for one month. In addition, during this home visit, multiple psychosocial instruments were administered and a self-estimate was obtained from the patient as to the likelihood of compliance with the medication regimen.

At the end of the month of treatment, the same member of the research staff returned to the patient's home and performed a pill count, an exit interview, and venipuncture for the repeated measurement of the serum ferritin level. The exit interview included questions regarding side effects experienced from the medication as well as the frequency of family reminders to comply with the prescribed regimen.

Measures

Self-esteem.—The Offer Self-Image Questionnaire for Adolescents, a 130-item scale, was used in this study to assess self-esteem. The questionnaire contains five subscales measuring constructs entitled "Psychological Self," "Social Self," "Familial Self," "Sexual Self," and "Coping Self." This scale has been validated across a wide variety of adolescent populations and has been found to be highly correlated with other measures of self-esteem in this age group, eg, the Tennessee Self-concept Scale.[2]

Locus of Control.—According to Rotter and colleagues[3] theory, persons with an internal locus of control view events as consequences of their own actions and, thereby, as being under their personal control. In contrast, externally controlled people view events as being unrelated to their own behavior and, therefore, beyond their control. The Children's Nowicki-Strickland Internal-External Control Scale[4] was used to assess locus of control in the present study. Containing 40 items, the Nowicki-Strickland



Derivation of final study group.

scale has been validated on a large number of children ranging from the third to the 12th grades. Normative demographic distribution of test scores is skewed, with lower scores reported in whites, persons of higher socioeconomic status, and older adolescents.[4] A lower score indicates a more internal locus of control.

Health Belief Model.—The major component areas of the Health Belief Model selected for examination in this study included (1) perceived severity of and future susceptibility to iron deficiency; (2) personal control over one's health; (3) general health motivation; (4) benefits of correcting the deficiency, eg, perceived efficacy of the medication; and (5) barriers to compliance that included expected ill effects of iron therapy as well as level of inconvenience in maintaining compliant behavior. As a research tool, the Health Belief Model has consistently accounted for a substantial amount of the variance in compliance among patients of all ages.[5]

Because there is no standardized test by which to measure a person's health beliefs, a modified Q-sort method was adapted by the us for use in the present study.[6] According to this technique, statements that reflected a specific health belief (eg, "I worry about my health a lot") were listed individually on separate 3 × 5 cards. All of the cards were shuffled before testing to achieve random order. In addition, a response tray, constructed with five slots labeled ordinally from "Sounds just like me" to "Doesn't sound like me at all," was used as a three-dimensional Likert scale. Each adolescent was presented with the stack of cards and instructed to place each card in the tray according to his degree of agreement with the health belief detailed on the card.

Intent to Comply.—Intent to comply was assessed during the first home visit by questionnaire, as follows: "How many days over the next week do you think you'll forget or be unable to take the medication?" Thus, the variable intent to comply was interval, with a potential score ranging from 0 to 7.

Compliance.—Throughout the entire study, two methods were employed as measures of compliance. First, pill counts were obtained during the final home visit and calculated as the percent of pills missing from the total number initially prescribed. Second, the differences between pretreatment and posttreatment serum ferritin levels were assessed. By this measure, compliance was defined as an increase in posttreatment ferritin levels to values exceeding 11 μg/L in female subjects and 18 μg/L in male subjects.

In addition, for each of the first 28 patients, weekly urine specimens were obtained at home for measurement of the level of riboflavin, 6 mg of which was included in each multivitamin-iron tablet. Because of the time commitment required to obtain the home urine samples and the high correlation between urinary riboflavin assay and home pill count in the first 28 patients, we elected to omit urine collection in the remaining 43 patients.

The urine samples were assayed for their riboflavin content by the method of Hobby and Deuschle.[7] In pilot studies, we determined that urinary riboflavin concentration increased fivefold to tenfold within one to four hours after ingestion of the vitamin tablet and returned almost to baseline levels within 24 hours. It was also previously established that individuals who consumed one pill per day had a measurable urinary riboflavin level whereas riboflavin could not be detected in the urine of individuals who were not receiving vitamin supplementation. Degree of compliance was defined as the percent of urine specimens testing positive for riboflavin.

Serum Ferritin.—Serum ferritin levels were measured by the enzyme immunoassay described by Worwood.[8] For the purposes of the present study, the definition of iron deficiency for girls was a ferritin level less than 12 μg/mL of serum and, for boys, a ferritin level of less than 19 μg/mL of serum. We employed a higher cutoff level for iron deficiency in boys because previous normative data clearly demonstrate higher levels of serum ferritin in adolescent male populations.[9] Because of the sensitivity of the ferritin method and the higher cutoff level in boys, the prevalence of iron deficiency (26%) reported here is higher than that reported in previous surveys.

Data Analysis

For individual statistical comparisons between psychosocial variables and compliance, Student's *t* tests and Pearson product-moment correlations were calculated. Regression analysis was performed to identify the relative contributions of the psychosocial variables in explaining compliant behavior. Analysis of variance was employed to compare the different methods of measuring compliance.[10]

RESULTS

Compliance Rates

The mean compliance rate in the final study group, as determined by home pill count, was 67% (SD, ±32%), ie, subjects, on average, took 67% of the prescribed regimen. There were no significant differences in compliance rates when the data were stratified according

Table 1.— Predictors of Repeated Ferritin Levels by Multiple Regression*

Independent Variable	Standardized Regular Coefficient	t	P
Initial ferritin level	0.62	7.56	<.0001
Home pill count	0.36	4.39	<.0001

*Total model $R^2 = 0.56$; $F = 42.03$; $P < .0001$.

Table 2.—Correlation of Psychosocial Variables With Compliance as Assessed by Individual Regression Analysis

Measure	R^2	F	P
Offer Self-Image Questionnaire	0.00	0.01	0.98
Nowicki-Strickland Internal-External Control Scale[4]	0.01	0.84	0.36
Health Beliefs Questionnaire	0.03	1.25	0.28
Control over health	0.06	4.86	0.03

to age, sex, race, or socioeconomic status. There was, however, a significant difference in the level of compliance according to the method of assessment. By home pill count, the mean compliance rate among the adolescents who also had home urine collection was 76% (SD, ±37%), compared with 61% (SD, ±20%) among those who did not ($t = -2.09$; $P < .05$).

The mean serum ferritin level before treatment was 10.6 μg/mL (SD, ±11 μg/mL), compared with a mean serum ferritin level after one month of treatment of 21.1 μg/mL (SD, ±15 μg/mL). When posttreatment ferritin levels were categorized into normal and low values, 59% of the final study group had normalized their iron stores without significant difference according to demographic background.

Comparing compliance measures, we found home pill counts to be significantly related to posttreatment ferritin levels, even after controlling for initial serum values. Table 1 details these relationships. Additionally, home pill counts correlated significantly with urinary assay ($r = .70$; $P < .001$) in the 28 patients who underwent both methods of assessment.

Biosocial Measures and Compliance

The mean score on the Offer Self-Image Questionnaire was 42.7 (SD, ±25), compared with a mean of 50 (SD, ±15) in other normal adolescent populations.[2] The mean score on the Nowicki-Strickland scale was 17 (SD, ±4), which also was not markedly different from normative data reported in other adolescent surveys. No significant differences were found between the variation in compliance and perceived levels of self-esteem and locus of control. Analyzing responses from the Health Belief Model, we found no significant correlation between perceived severity of iron deficiency or perceived benefits or costs of treatment and the subjects' adherence to the regimen of oral iron therapy. The only personal health belief that contributed significantly to the variance in compliant behavior was subjective control over one's health in general (Table 2).

Individual variables with significant correlation with compliance are presented in the following tabulation.

Variable	r	P
Reported side effects	−.47	<.01
Initial self-assessment	−.30	<.01
Frequency of family reminders	.31	<.01

Adverse side effects, primarily gastrointestinal tract irritation, occurred in 16% of the final study group and were significantly correlated in a negative fashion with compliance. At the initiation of therapy, patients predicted that over the following week they would "forget" or "be unable" to take the medication an average of 0.69 days (SD, ±0.94 days). No one predicted more than three days of noncompliance. Reported intent to comply was a significant predictor of compliance, as measured by home pill counts. Finally, during the final home interview, 64% of the study group stated that they had received reminders from family members to take the medication "all of the time" or "most of the time." Higher frequency of family reminders was significantly related to increased compliance.

COMMENT

The 67% mean compliance rate found in this group of adolescents was high compared with that found in most previous studies.[1,11] This finding may be due to several factors. First, the adolescents reported a high frequency of family reminders to take the medication. Although there have been no previous studies assessing the effects of family reminders on compliance using our exact format, two reports have demonstrated that the degree of effective parental involvement is significantly related to compliance in adolescents with or without chronic disease.[12,13] Second, side effects of the multivitamin preparation, a significantly negative predictor of compliance, were found in only 16% of the final study group. The occurrence of adverse side effects, particularly disfiguring changes (eg, hair loss and hirsutism), has been reported as a powerful predictor of noncompliance in adolescents receiving various kinds of chemotherapy.[14,15] Third, there was evidence of a policing effect, ie, the positive effect on a target behavior due to increased supervision by research staff.[16] Those adolescents who received four extra home visits for the purpose of urine collection had a significantly higher compliance rate, by home pill count, than the rest of the final study group. This difference in behavior may have resulted from either patient knowledge as to the purpose of urine testing or from positive reinforcement inherent in increased telephone and home contact. On exit interview, 32% of the subgroup guessed correctly the purpose of urine testing; however, there was no significant difference between knowledge and compliance levels. Thus, we conclude that the skewed results in this subgroup were due to increased contact with the research staff.

Contrary to previous reports derived from adolescents with chronic illness,[14,17-19] we found no significant influence of self-esteem, locus of control, and most facets of the Health Belief Model

on the level of compliance. The lack of an association between self-esteem and locus of control with compliance in this group of asymptomatic adolescents may reflect different developmental dynamics in healthy adolescents vs teenagers with chronic illness. The negative findings between personal health beliefs and compliance in our study may be due to limitations of our method of assessment. Another explanation is that iron deficiency is an asymptomatic, relatively nonthreatening medical condition that is insufficient to mobilize conviction ("cue to action") regarding its severity and the perceived benefits of curative treatment. The one aspect of the Health Belief Model that, on multiple regression analysis, did correlate significantly with compliance was subjective control over one's health in general. Interestingly, the other measure of perceived control, the locus of control construct, showed no significant relationship with compliant behavior. This negative finding may have been due to the difficulty reported by study patients in interpreting the test questions of the Nowicki-Strickland Internal-External Control Scale.

Three significant psychosocial determinants of compliance included those relatively alterable by behavioral intervention. Since side effects were highly related to noncompliance, initial patient instruction to help minimize and warn against adverse reactions may increase adherent behavior. In addition, as has been demonstrated in previous studies,[20,21] a patient's initial reported intent to comply is a strong predictor of later compliance. This finding provides a simple tool by which to measure adherence and provides an immediate forum for intervention. The strong correlation between frequency of family reminders and compliance with an oral iron therapy regimen is interesting in light of the general assumption that adolescents should assume autonomy in administration of medication to protect their need for increased independence from the family. As stated previously, effective parental involvement (ie, participating in management of clinical situations) has been demonstrated to be important in enhancing compliance in adolescents.[12,13] However, dysfunctional interaction within the family has been reported to be a significant deterrent to compliance with prescribed medical regimens in adolescents with certain chronic diseases.[14,22] It may be that simple iron deficiency is dissimilar from chronic illness that often involves long-term conflictual issues of dependency. Our findings suggest that, in the case of a benign medical condition, family reminders are helpful in enhancing compliance.

The home pill count, when compared with the direct methods of urinary and blood assay, was an accurate measure of compliance in this study. Since direct measures, such as blood levels, are not available for many drug regimens, and since weekly home urine collection is time-consuming, we recommend post-treatment home pill count as a useful alternative tool of assessment.

In summary, possible effective interventions to enhance compliance that could be implemented during an office visit include a brief interview of the patient's perceived future compliance as well as preferential choice of medications with fewer adverse side effects and a forewarning of any side effects associated with the proposed therapeutic regimen. Finally, enlisting a supportive parent to remind the patient of the medication schedule (and, in some circumstances, actual administration of the medication) may be very effective in enhancing compliant behavior.

This study was supported in part by the Children's Hospital Research Foundation, Columbus, Ohio, grant 74-020, and the Roessler Foundation, Ohio State University College of Medicine, Columbus.

We would like to thank Stanford Friedman, MD, for his guidance in the design of this study and Thelma Campbell and William Hritsko for their attention and care in preparing the manuscript.

References

1. Jay S, Litt IF, Durant RH: Compliance with therapeutic regimens. *J Adolesc Health Care* 1984;5:124-136.

2. Offer D: *The Adolescent: A Psychological Self-portrait*. New York, Basic Books Inc, 1981.

3. Rotter JB, Seeman M, Liverant S: Internal vs external control of reinforcements: A major variable in behavior therapy, in Washburne NF (ed): *Decisions, Values and Groups*. Elmsford, NY, Pergamon Press Inc, 1962, pp 473-516.

4. Nowicki S, Strickland BR: A locus of control scale for children. *J Consul Clin Psychol* 1973;40:148-154.

5. Janz NK, Becker MH: The health belief model: A decade later. *Health Educ Q* 1984;11:1-47.

6. Gayton WF, Friedman SB, Tavormina JF, et al: Children with cystic fibrosis: I. Psychological test findings of patients, siblings and parents. *Pediatrics* 1977;59:888-894.

7. Hobby GL, Deuschle KW: The use of riboflavin as an indicator of isoniazid ingestion in self-medicated patients. *Am Rev Respir Dis* 1959;80:415-425.

8. Worwood M: Serum ferritin, in Cook JD (ed): *Methods of Hematology*. New York, Churchill-Livingston Inc, 1980, vol 1, pp 59-89.

9. Alfrey CP: Serum ferritin assay. *CRC Crit Rev Clin Lab Sci* 1978;9:179-208.

10. Lapin LL: *Statistics: Meaning and Method*, ed 2. New York, Harcourt Brace Jovanovich Inc, 1980.

11. Dunbar J: Compliance in pediatric populations: A review, in McGrath PJ, Firestone P (eds): *Pediatric and Adolescent Behavioral Medicine Issues in Treatment*. New York, Springer Publishing Co Inc, 1983, pp 210-231.

12. Tebbi CK, Cummings KM, Zevon MA, et al: Compliance of pediatric and adolescent cancer patients. *Cancer* 1986;58:1179-1184.

13. Irwin CE, Millstein SG, Shafer MAB: Appointment-keeping behavior in adolescents. *J Pediatr* 1981;99:799-802.

14. Korsch BM, Fine RN, Negrete VF: Noncompliance in children with renal transplants. *Pediatrics* 1978;61:872-876.

15. Dolgin MJ, Katz ER, Doctors SR, et al: Caregivers' perceptions of medical compliance in adolescents with cancer. *J Adolesc Health Care* 1986;7:22-27.

16. Ingelfinger JA, Mosteller F, Thibodeau LA, et al: Reading a report of a clinical trial, in *Biostatistics in Clinical Medicine*. New York, Macmillan Publishing Co Inc, 1983, pp 223-242.

17. Heinzelmann F: Factors in prophylaxis behavior in treating rheumatic fever: An exploratory study. *J Health Hum Behav* 1962;3:73-81.

18. Litt IF, Cuskey WR, Rosenberg A: Role of self-esteem and autonomy in determining medication compliance among adolescents with juvenile rheumatoid arthritis. *Pediatrics* 1982;69:15-17.

19. Jamison RN, Lewis S, Buish TG: Cooperation with treatment in adolescent cancer patients. *J Adolesc Health Care* 1986;7:162-167.

20. Litt IF: Know thyself: Adolescents' self-assessment of compliance behavior. *Pediatrics* 1985;75:693-696.

21. Davis MS: Physiologic, psychological and demographic factors in patient compliance with doctors' orders. *Med Care* 1986;6:115-122.

22. Macdonald ME, Hagberg KL, Grossman BJ: Social factors in relation to participation in follow-up care of rheumatic fever. *J Pediatr* 1963;62:503-513.

Household Electrical Injuries in Children

Epidemiology and Identification of Avoidable Hazards

M. Douglas Baker, MD, Christine Chiaviello, MD

• The medical records of all children with household electrical injuries were reviewed. The children were seen from 1980 to 1986 at The Children's Hospital of Philadelphia and The Johns Hopkins Hospital, Baltimore. Injuries occurred predominantly in children younger than age 6 years, most commonly while meals were being prepared. The most frequent cause of injury was oral contact with electrical cords or cord sockets, or contact with wall sockets either directly or via conductive foreign objects such as keys or pins. Data reported to the Consumer Product Safety Commission were also analyzed and corroborated our findings. We suggest a series of prevention strategies based on these data. A new wall outlet cover design is described.

(*AJDC* 1989;143:59-62)

Although electrical injuries in children are very common, few studies have identified the causes of such injuries.[1] Previous investigation has demonstrated that fewer injuries occur in families who recognize and protect their children from identified hazards,[2] and that physicians can effect a decrease in the incidence of injuries through appropriate parental counseling.[3] The purpose of this study was to examine factors involved in household electrical injuries in children.

PATIENTS AND METHODS

We reviewed medical records of all children presenting to the Emergency Department of The Children's Hospital of Philadelphia (CHOP) and to the Pediatric Emergency Department of The Johns Hopkins Hospital (JHH), Baltimore, from 1980 through 1986 for evaluation of electrical injuries. Cases were identified using both computerized listings by diagnosis and audit of daily Emergency Department records. The information extracted included demographic data, month of injury, details of the injury scenario, treatment, disposition, and complications.

We gathered additional data from the National Electronic Injury Surveillance System regarding childhood electrical injuries reported to the Consumer Product Safety Commission (CPSC) during the same period. The National Electronic Injury Surveillance System collates data from over 60 emergency rooms throughout the country. Specifically, we noted the age, sex, type of injury, and involvement of foreign objects as electrical conductors. Because fewer details were available for CPSC cases, these data are presented separately.

RESULTS

CHOP and JHH Data

A total of 144 patients (86 at CHOP and 58 at JHH) were studied. Based on the total number of visits to each institution, these injuries occurred at a rate of one per 5500 visits. Males outnumbered females in a ratio of 1.7:1. Most patients (82%) were black. This racial distribution does not significantly deviate from the overall figures for these two emergency departments. The mean age was 5.1 years; mode, 2 years. Sixty-eight percent of all patients were younger than age 6 years (Fig 1).

Based on emergency department census data, actual injury rates vary from those expected for both younger and older age groups. While children younger than age 6 years represent 39% of all visits, they incur 68% of these injuries. Conversely, children older than age 9 years represent 36% of all visits, and incur 17% of household electrical injuries. United States Census[4] data (1980) approximate our Emergency Department census data. Children younger than age 5 years make up 32% of all US children younger than age 15 years, while those ages 10 to 14 years represent 36% of the total.

There was no notable seasonal variation in the occurrence of electrical injuries. Warm-weather months were as well represented as those during which children are more typically confined indoors. In contrast, the time of injury varied appreciably throughout the day (Fig 2). The hours of peak incidence were 10 AM through noon and 4 PM through 6 PM.

The majority (82%) of injuries incurred were burns; 18% were shocks. Of the burns, 31% were superficial only; the remainder were at least in part second-degree (n=53; 45%) or third-degree (n=28; 24%) injuries. Seventy-nine percent of third-degree burns

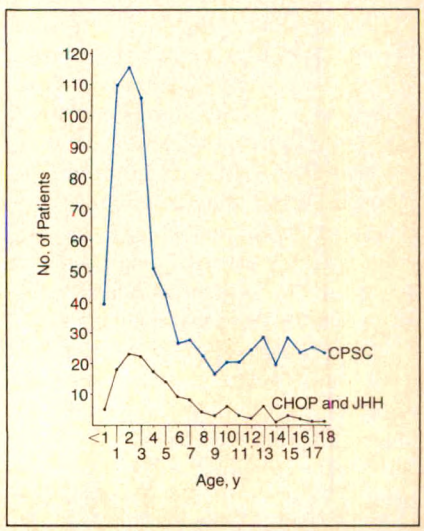


Fig 1.—Distribution of household electrical injuries by age. CPSC indicates Consumer Product Safety Commission; CHOP, The Children's Hospital of Philadelphia; and JHH, The Johns Hopkins Hospital.

Accepted for publication Sept 19, 1988.

From the Division of General Pediatrics, Department of Emergency Medicine, The Children's Hospital of Philadelphia (Dr Baker); the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia (Dr Baker); and the Department of Pediatrics, The Johns Hopkins Hospital, Baltimore (Dr Chiaviello).

Reprint requests to the Emergency Department, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Baker).

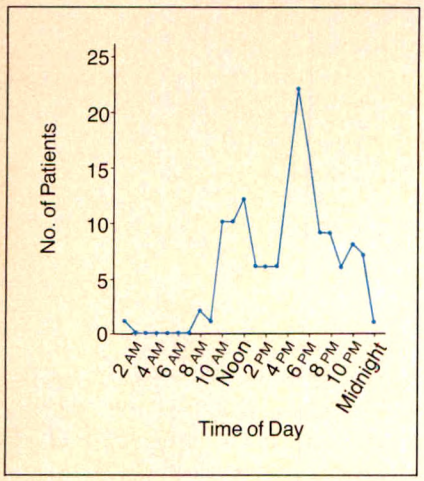


Fig 2.—Occurrence of household electrical injuries by time of day for patients at The Children's Hospital of Philadelphia and The Johns Hopkins Hospital.

Table 1.—Activities Leading to Injury*

Activity	No. (%) CHOP	JHH	Total	Complications
Biting cord or cord socket	20	20	**40** (28)	17 (43)
Foreign object in wall socket	24	16	**40** (28)	2 (5)
Faulty wall socket or cord plug	15	9	**24** (17)	5 (21)
Faulty cord	17	6	**23** (16)	0
User fault	10	7	**17** (12)	7 (41)
Total	**86**	**58**	**144**	**31**

*CHOP indicates The Children's Hospital of Philadelphia; and JHH, The Johns Hopkins Hospital.

involved children younger than age 6 years. Twenty-six of 28 third-degree burns resulted from some sort of oral contact with the electrical source; two involved foreign objects. Thirty-one burns developed complications, including scarring (n=26; 18%), infection (n=2; 1%), and tissue loss requiring grafting (n=2; 1%). Both injuries requiring grafting resulted from children biting on cords. Fourteen children required admission to the hospital for an average of 2.6 days (range, one to five days).

Most burns involved the hands (57%) or face (35%). The rest were located on the lower extremities (5%), arms (2%), and chest (1%). Of the 44 facial injuries, eight affected the lip commissures. Commissure injuries accounted for 62% of the total number of admissions.

The actions leading to injury are depicted in Table 1. Most injuries occurred as a result of oral contact with electrical cords (28%) or placing foreign bodies in sockets (28%). Contact with faulty sockets or plugs (17%) and frayed or cracked cords (16%) were next most frequently cited. User faults accounted for the remainder of injuries. These included unplugging by pulling on the cord, rather than the plug, with either the hand (6%) or teeth (4%); cutting a cord with a tool (2%); and playing with a light socket (1%).

Forty-one injuries (28%) treated at CHOP or JHH resulted from foreign objects being placed in wall sockets (Table 2). Most common among these were pins (24%) and keys (22%). Bare fingers were also included in this category and made up a significant portion (12%) of the total. Although not recorded in the medical records, it is likely that some of these bare-finger injuries involved missing or faulty socket covers. Three of the 41 foreign object–related injuries occurred after plastic safety plugs were removed from the wall outlets by the children injured. All three children were 2 years old.

Table 2.—Foreign Objects Placed in Wall Sockets*

Object	No. of Cases CHOP	JHH	CPSC	Total, No. (%)
Barette	0	0	3	**3**
Brush handle	0	1	0	**1**
Coin	0	0	1	**1**
Cup	1	0	1	**2**
Drapery hook	1	0	1	**2**
Finger	3	2	31	**36** (16)
Foil	0	0	1	**1**
Hanger	1	0	2	**3**
Key	5	4	57	**66** (30)
Metal scrap	0	0	4	**4**
Nail	0	0	1	**1**
Paper clip	1	3	6	**10** (4)
Pin	6	4	48	**58** (26)
Ruler edge	1	0	1	**2**
Scissors	2	1	2	**5**
Screw	1	0	1	**2**
Screwdriver	0	0	1	**1**
Silverware	0	0	4	**4**
Stick	1	0	1	**2**
Toy car	0	0	1	**1**
Tweezers	0	0	4	**4**
Wire	2	1	11	**14** (6)
Total	**25**	**16**	**182**	**223**

*CHOP indicates The Children's Hospital of Philadelphia; JHH, The Johns Hopkins Hospital; and CPSC, Consumer Product Safety Commission.

CPSC Data

A total of 762 electrical injuries were reported to the CPSC during the study period. Of these, 174 (23%) were listed as shocks, and 588 (77%) as burns. Males outnumbered females in a ratio of 1.4:1. The mean age was 5.9 years; mode, 2 years.

Of the 762 injuries reported, 182 (24%) involved foreign objects in electrical sockets. Keys, pins, and bare fingers represented 74% of all foreign objects named. In some instances, faulty or absent wall plates might have permitted insertion of larger objects, such as fingers. When compared with all other children who placed foreign objects into sockets, children less than age 1 year and over age 6 years used such foreign objects at significantly lower rates than expected ($P<.025$ and $P<.0001$, respectively). Conversely, children in the 1- to 4-year age range placed foreign objects into sockets more often than others ($P<.0001$). Of the 182 foreign object–related injuries, 156 (86%) involved children 4 years old or younger.

COMMENT

Few studies have addressed the issue of household electrical injuries in children. Jay et al[5] reported that only a small percentage (4%) of all burns in children less than 17 years old were due to an electrical source. Our data also indicate a low overall occurrence of this type of injury. Household electrical injuries (one per 5500 visits) were far less frequent events than other injuries, such as human bites (one per 600 visits) or lacerations (one per 20 visits), that

occurred during the same periods. Viewed in this manner, however, these figures may be misleading. Our data indicate that more than two thirds (68%) of all injuries involve children younger than age 6 years. Household electrical injuries represent a significantly larger proportion of all visits within this age group than in the study group as a whole. This group has the greatest potential for extended morbidity.

Others have noted that electrical burns are not very common or severe,[6] ie, few require hospitalization. Although it is true that most of our study population did not require admission, more than two thirds incurred second-degree (45%) or third-degree (24%) burns and 22% developed significant complications. The occurrence of any one of these injuries substantiates our attempts to understand and prevent their future occurrence.

We have identified several important epidemiologic trends. As is the case in many other types of injuries (notably, poisonings and lacerations),[7] household electrical injuries most commonly involve preschool-age children, whose curiosity and acquisition of developmental milestones might be contributory factors. This is exemplified by the toddler who mimics older family members' use of keys by placing them in the narrow slots of wall outlets, or by the young child who pursues oral exploration of his environment by placing a frayed electrical cord into his mouth. Both of these types of injuries occurred most frequently in children between ages 1 and 3 years. The finding that most (79%) third-degree burns occur in children younger than age 6 years further highlights the importance of proper supervision and injury prevention in this age group.

Although injuries occurred during all hours of usual daily activity, two intervals of peak incidence were noted. These are similar to those reported for electrical injuries in Scottish children[8] and coincided with typical food preparation times, during which supervision of children might be less vigilant. This concept is supported by the fact that 88% of foreign object–related injuries occurred during these hours, compared with 53% of injuries not involving foreign objects in wall sockets. Similarly, 60% of oral contact injuries occurred during food preparation times.

The activities leading to injury deserve close scrutiny. Others[6,9-11] have indicated that biting electric cords and sucking on extension cord sockets are the most common causes of electrical burns in children admitted to the hospital. Our data support this observation. Twenty-eight percent of our patients, including nine of 14 children requiring admission to the hospital, were injured in this way. Furthermore, 71% of all complications resulted from oral contact with electrical sources. These data underscore the importance of counseling families regarding electrical safety, and of advocating improved product design.

A significant source of injury in our study population was the household wall socket. While only two of our 14 admissions were included in this group, more than 40% of all injuries involved a wall socket; 82% of these resulted in either second- or third-degree burns. These data are not surprising, given the disproportionately frequent occurrence of electrical injuries in young children. Sockets are at waist level and within easy reach of these children, who have recently mastered the ability to cleanly insert objects into and remove them from small slots. Our data might cause one to reconsider the advice provided in a previous article that "health education should address more relevant issues."[4]

The majority of wall socket injuries at CHOP and JHH involved the placement

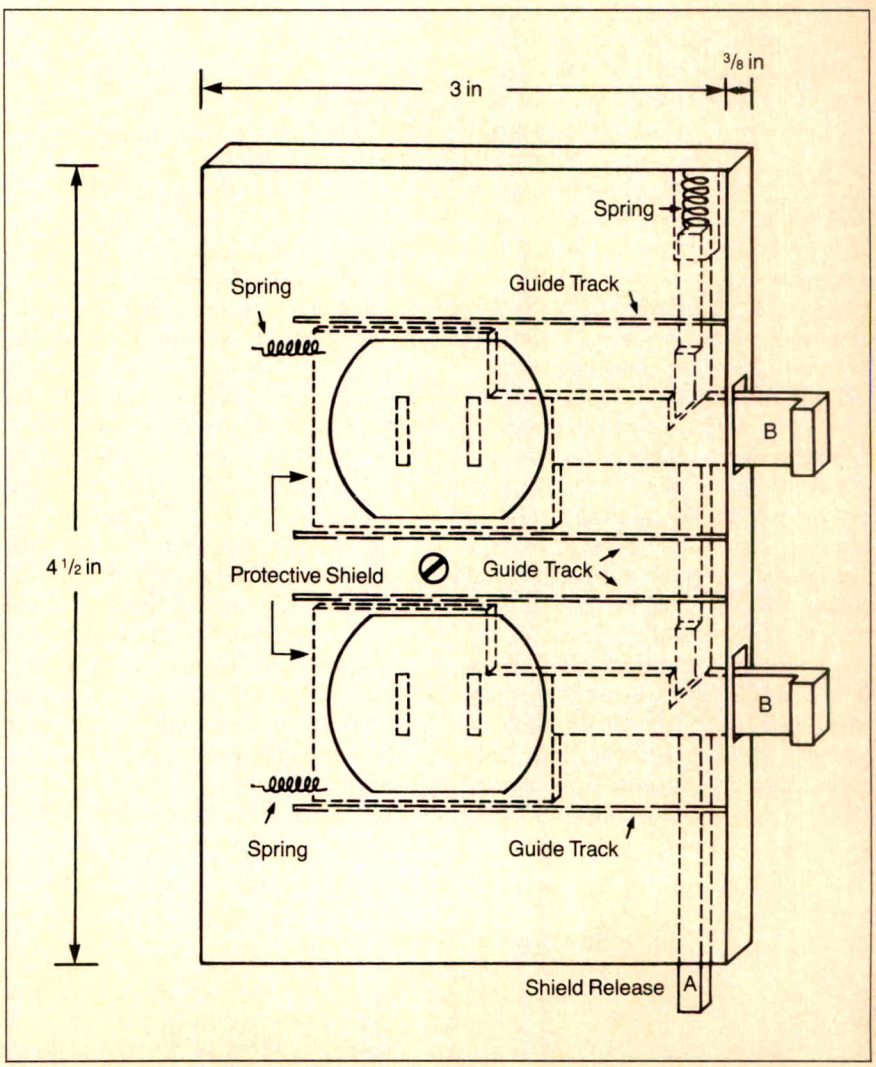


Fig 3.—Proposed wall socket cover (patent applied for). Operation instructions: (1) push release bar A upward; (2) slide protective cover B to right; (3) insert plug.

of foreign objects into them. This finding prompted us to review CPSC data, which further established several household items as common offenders. The two most frequently utilized objects were keys and pins. Of the latter, 66% were "bobby pins," which many might not recognize as potentially harmful. Keys are similarly viewed in this manner, as evidenced by the fact that infant toys are often manufactured in these shapes and that automobile and other keys are often offered to infants as toys. Indeed, by furnishing these items to our children, we might be inadvertently contributing to the potential for injury. Nevertheless, many of these injuries might have been avoided by the use of effective nonremovable wall socket covers.

One further area of concern is the number of injuries attributed to faulty electrical cords. These injuries occur as a result of hand or foot contact with frayed cords, some of which have been inadequately repaired with electrical tape. It is incumbent on parents to recognize both the fire and health hazards these damaged items present.

Our observations lend themselves to several prevention strategies. They reinforce the importance of discussing with parents the potential hazards of electrical cords (both intact and frayed) and cord sockets. They further support the efforts of physicians to urge parents to cover unused sockets, to be cognizant of the need for proper supervision during times that are typically busy at home, and to restrict the availability of small metallic objects to small children.

The data also suggest that further consideration should be given to the product design of toys intended for infants and of household electrical equipment. Infant toys should not simulate common household items that have been frequently identified as foreign bodies or other vectors of injury. Electrical equipment must be sturdily constructed of durable materials, and incorporate a minimum of accessible connections to prevent contact of saliva with electrical current. Sealed single-unit cord-plug or cord-socket (extension cords) combinations are good examples of this design.

Inspired by the failure of plastic wall socket plugs to prevent electrical injuries in several 2-year-old children, we have developed a new wall outlet cover design (Fig 3). This cover is intended to replace existing wall outlet plates and incorporates independently acting thin plastic outlet shields, which completely cover the sockets. These shields are released by a two-step procedure that would be difficult for small children to accomplish without the use of both hands. The shields are spring-loaded and automatically close on release of the shield handle or after unplugging. The cover is made of inexpensive materials and involves few moving parts. This model has not been completely tested and is not available at present.

This wall cover design has several advantages over the currently available plastic socket plugs. Unlike the latter devices, the plastic shields are not removable and therefore cannot be misplaced. Instead, they become a permanent part of the wall outlet once the cover is screwed into place. Second, the automatic shield closure eliminates the effort required to replace socket plugs, which is less likely to occur when they are removed by young children. Finally, the two-step release procedure requires diligent effort on the part of the child to be successful. A three-step procedure is required to place an object into the exposed outlet. Furthermore, the shield must be held open to allow placement of an object into the socket. This combination of events is difficult for a toddler or young child to master.

We conclude that household electrical injuries are significant sources of childhood morbidity, particularly in children younger than age 6 years. The preventability of these injuries transforms their relatively low overall incidence into one that is unacceptably high. Several prevention strategies have been developed, including single-unit molding of electrical cords and plastic inserts for unused sockets. The continued occurrence of electrical injuries suggests that these measures have not been entirely effective. Indeed, three injuries in our study group followed removal of socket safety caps by 2-year-old infants. Product designs can be improved; an example has been provided. Further development of durable, safe materials is needed, followed by properly designed intervention trials.

The authors thank Sally E. Moore and Randi Bell for their help in gathering the data presented in this report, and Rose Beato for her careful preparation of the manuscript.

References

1. Data released by the National Center for Health Statistics, Scientific and Technical Branch: Division of Vital Statistics. US Dept of Health, Education and Welfare, Public Health Service, Office of Health Research, Statistics and Technology, 1980.
2. Dershewitz RA: Will mothers use free household safety devices? *AJDC* 1979;133:61-64.
3. Feldman KW: Prevention of childhood accidents: Recent progress. *Pediatr Rev* 1980;2:76-81.
4. US Department of Commerce, Bureau of the Census: *1980 Census of Population.* Government Printing Office, 1984, vol 1, pp 1-7.
5. Jay KM, Bartlett RH, Danet R, et al: Burn epidemiology: A basis for burn prevention. *J Trauma* 1977;17:943-947.
6. Young TL, Reisinger KS: Wall socket electrical burns. *Pediatrics* 1980;65:825-827.
7. Rivara FP, Bergman AB, LoGerfo JP, et al: Epidemiology of childhood injuries: II. Sex differences in injury rates. *AJDC* 1982;136:502-506.
8. Robinson SS: The causes of burns of children in Scotland. *Br J Plast Surg* 1968;21:140-146.
9. Thompson H, Tuckes A, Farmer A: Electrical burns to the mouth in children. *Plast Reconstr Surg* 1965;35:466-477.
10. Ortiz-Monasterio F, Facter R: Early definitive treatment of electric burns of the mouth. *Plast Reconstr Surg* 1980;65:169-176.
11. Gifford GH, Marty A, MacCollum D: The management of electrical mouth burns in children. *Pediatrics* 1971;47:113-119.

Quotables:

Advertisements: *Medical journals now contain more advertisements for books which purport to teach the physician to pass a multiple-choice examination than books which will teach him to examine a patient.*

JOSEPH D. SAPIRA
Perspectives in Biology and Medicine 1982

Differential Effects of Intrauterine and Postnatal Brain Growth Failure in Infants of Very Low Birth Weight

Maureen Hack, MB, ChB; Naomi Breslau, PhD; Avroy A. Fanaroff, FRCPE, DCH

• We investigated the contribution of brain growth failure to outcome in infants of very low birth weight (VLBW; <1.5 kg) who were appropriate for gestational age (AGA; n = 379) or small for gestational age (SGA; n = 102). Growth was assessed at birth, term, and 8 and 20 months' corrected age and results of a Bayley Mental Developmental Index (MDI) and neurologic examination were evaluated at 20 months of age. Both groups had similar 20-month MDI scores (93 vs 90) and similar rates of neurologic impairment (14% vs 10%). More SGA infants (25%) than AGA infants (14%) had a subnormal head circumference at 8 months' corrected age, indicating failure to catch up in head growth. Subnormal head size at 8 months predicted the 20-month MDI score for both groups. However, multivariate analysis indicated that, whereas subnormal 8-month head size was directly associated with the MDI score in AGA children, in SGA children 8-month head size was not significantly related to the MDI score when neonatal illness, neurologic impairment, socioeconomic status, and race were controlled for. We conclude that in AGA VLBW infants, subnormal head size at 8 months results from major neonatal illness and has adverse later effects. In SGA infants, subnormal head size at 8 months has many causes, including growth retardation in utero, which may not have an adverse effect on outcome; if subnormal head size is superimposed with neonatal illness, a poorer outcome is likely.

(*AJDC* 1989;143:63-68)

Infants of very low birth weight (VLBW; <1.5 kg) constitute a heterogeneous population with regard to both their intrauterine and postnatal growth. Twenty percent of VLBW infants are small for gestational age (SGA; birth weight < −2 SDs for gestational age) after severe intrauterine growth failure, while many VLBW infants who have normal intrauterine growth and are thus appropriate for gestational age (AGA) at birth fail to grow adequately during the neonatal period.[1] As part of a longitudinal study of the prognostic importance of catch-up growth, we found that among AGA VLBW infants who failed to grow adequately during the neonatal period, the persistance of a subnormal head circumference at 8 months' corrected age, ie, failure to catch up in brain growth, significantly influenced the 3-year IQ, even when other biologic and sociodemographic variables were controlled for.[2] We became intrigued by the fact that AGA and SGA VLBW infants had similar early childhood outcomes,[3-8] despite the fact that SGA infants had lower rates of catch-up brain growth.

To compare the differential effect of brain growth failure on outcome among SGA and AGA VLBW infants, we examined the effect of failure to catch up in head circumference by 8 months' corrected age on the 20-month Bayley Mental Developmental Index (MDI) when sociodemographic and biologic variables were controlled for.

PATIENTS AND METHODS

Population

The study population was drawn from 1026 VLBW infants admitted to the Neonatal Intensive Care Unit, Rainbow Babies and Childrens Hospital, Cleveland, from January 1977 through December 1982. Five hundred ninety-three children (58%) survived to their second year. Thirty-six (6%) were unavailable for follow-up and growth and/or developmental data on 76 (13%) were incomplete, leaving 481 (81%) children for the analysis. Of this population, 379 (79%) were born AGA and 102 (21%) were born SGA (< −2 SDs for age).[9] A five-year cohort was examined to obtain sufficient SGA infants for meaningful analyses.

Methods

The method of follow-up has been previously described.[8]

Antepartum, intrapartum, and neonatal risk factors were measured by the method of risk assessment described by Hobel and colleagues.[10]

Growth parameters were measured at birth and then longitudinally at 40 weeks' (the expected term date) and 8 and 20 months' corrected age (postmenstrual plus postnatal age). The infants were classified as AGA or SGA in birth weight (< −2 SDs) using Usher's tables of intrauterine growth at sea level.[9] They were then categorized as either normal or subnormal in head circumference (less than 2 SDs below the mean for age) at each of the time points.[11] The definition of head circumference as a binary variable (normal vs subnormal) rather than as a continuous variable was based on our own analyses and those of others indicating that the effect of brain growth on intelligence is not linear, but rather is related to extreme deviations.[2,12]

Neurosensory impairment included hypotonia, cerebral palsy (spastic diplegia, hemiplegia or quadriplegia), hydrocephalus, or severe visual or hearing impairment and was assessed at 20 months' corrected age. Social class was measured by the two-factor Hollingshead index, which ranges from 1 (high) to 5 (low).[13] Race was described as either black or white.

The Bayley Scales of Infant Development,[14] including motor and mental performance, were performed at 20 months' corrected age. Since the MDI score correlates best with later IQ, this measure was used for outcome analyses.

Analysis of Data

We present first the comparisons of AGA and SGA populations on demographic, perinatal, and developmental variables. The statistical significance of the differences between group means were tested by *t* tests

Accepted for publication Oct 18, 1988.

From the Department of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland.

Reprint requests to Rainbow Babies and Childrens Hospital, University Hospitals of Cleveland, 2101 Adelbert Rd, Cleveland, OH 44106 (Dr Hack).

and between-group proportions were obtained by the χ^2 test. The associations between the 20-month MDI score and head circumference at various ages (ie, birth, 40 weeks, 8 months, and 20 months) were estimated by η^2 (eta) and their significance was tested by the F statistic. η^2 Measures the proportion of explained variance in the dependent variable and is analogous to R^2, except that the independent variable is categorical rather than continuous.[15]

Because the analysis is exploratory, rather than a test of a hypothesis, we present the α level for each individual test, but we did not calculate overall significance tests that correct for multiple comparisons.

To test and estimate the unique effect of subnormal 8-month head circumference on the 20-month MDI score, we used hierarchical multiple regression analysis in which other biologic and social variables were included. A separate analysis was performed for the AGA and for the SGA populations.

RESULTS

Comparison Between AGA and SGA Infants

Demographic and Perinatal Risk Factors.—There were no significant differences in the maternal demographic characteristics. (Results are given as the mean ± SD). However, more mothers of SGA infants tended to be unmarried and black. One hundred sixty-one (42%) of mothers of AGA infants were unmarried and 213 (56%) were black, compared with 52 (51%) mothers of SGA infants who were unmarried and 68 (67%) who were black. Forty-one percent and 44% of mothers of AGA and SGA infants, respectively, were in Hollingshead Social Class V. The SGA infants had a significantly greater gestational age ($P<.001$) and significantly lower birth weight ($P<.002$) compared with AGA infants. Among SGA infants the mean birth weight was 1126 ± 261 g and the mean gestational age was 32.0 ± 3 weeks, compared with a birth weight of 1204 ± 200 g and gestational age of 29.3 ± 2 weeks among the AGA infants. Head circumference was 26.5 ± 2.1 cm at birth in the SGA infants and 26.6 ± 1.8 cm in the AGA infants. Fifty percent of the infants in each group were male. Although group differences were not significant, more SGA infants were of multiple birth (24 [24%], compared with 57 [15%] of AGA infants).

Table 1 presents scores (obtained by the method of Hobel and colleagues[10]) for antepartum, intrapartum, and neonatal risk and comparisons for specific individual perinatal risk factors. No overt intrauterine infections were diagnosed. Mothers of SGA infants had significantly higher antepartum and intrapartum risk scores, partly because of a higher rate of pregnancy hypertension. The AGA infants had significantly higher neonatal risk scores, predominantly the result of a lower 5-minute Apgar score and a higher incidence of respiratory distress syndrome and apnea of prematurity.

Table 1.—Mean Risk Scores and Perinatal Risk Factors of Appropriately Grown (AGA) and Small for Gestational Age (SGA) Infants

	Group		
	AGA (n = 379)	SGA (n = 102)	P
Mean (± SD) Hobel and colleagues[10] risk score			
Antepartum	10.8 ± 12	14.7 ± 12	<.005
Intrapartum	16.2 ± 12	18.9 ± 11	<.05
Neonatal	57.9 ± 37	47.2 ± 34	<.01
Antepartum and intrapartum risk factors, No. (%) of infants			
Pregnancy hypertension	33 (9)	30 (29)	<.0001
Premature rupture of membranes	116 (31)	24 (24)	Not significant
Antepartum bleeding	71 (18)	20 (21)	Not significant
Neonatal Risk Factors, No. (%) of infants			
Apgar score <6 at 1 min	218 (58)	49 (48)	Not significant
Apgar score <6 at 5 min	97 (26)	14 (14)	<.02
Respiratory distress syndrome	257 (68)	43 (42)	<.0002
Apnea of prematurity	201 (53)	34 (33)	<.0005

Table 2.—Comparison of MDI Scores and Impairment Rates Among AGA and SGA Infants*

	Group	
	AGA (n = 379)	SGA (n = 102)
Mean (± SD) 20-mo MDI	92.8 ± 18	89.9 ± 17
Major congenital malformation, No. (%) of infants	5 (1.3)†	2 (2)‡
Neurosensory impairment, No. (%) of infants§	52 (14)	10 (10)
Neurologic	41 (11)	6 (6)
Cerebral palsy	30 (8.0)	3 (3)‖
Hydrocephalus	6 (1.6)	1 (1)
Seizure	2 (0.5)	1 (1)
Hypotonia	3 (0.8)	1 (1)
Visual	6 (1.6)	4 (4)
Hearing	5 (1.3)	. . .

*MDI indicates Bayley Mental Developmental Index[14]; AGA, appropriate for gestational age; and SGA, small for gestational age.

†Includes congenital neuropathy, congenital hydrocephalus, Down's syndrome, duodenal atresia, and cleft lip and palate.

‡Includes extreme microcephaly and chorioretinitis and multiple minor malformations.

§Excluding children with congenital malformations.

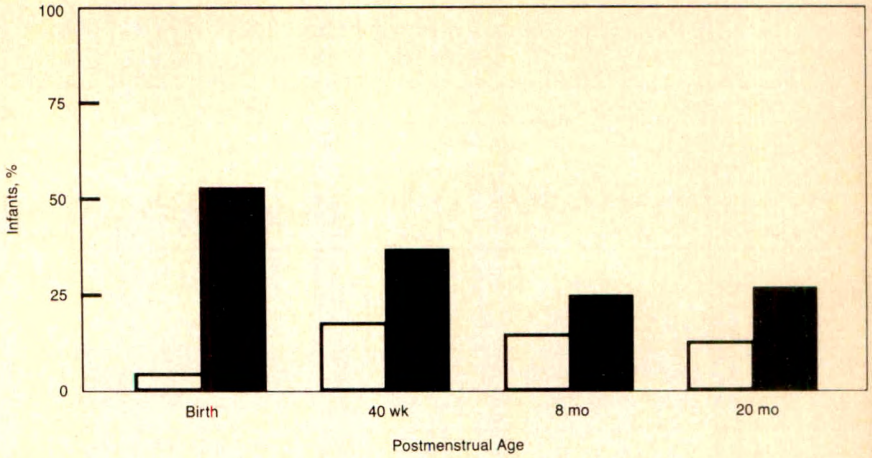
‖$\chi^2 = 3.11$; $P<.01$.

Neurodevelopmental Outcome.—As shown in Table 2, the differences between the mean MDI scores of AGA and SGA infants were not significant, and neither was the incidence of major congenital malformations or neurosensory impairment. However, AGA children had a higher incidence of cerebral palsy (8% vs 3%; $P<.01$) than SGA children. Visual impairment in all cases was due to severe retinopathy of prematurity.

Physical Growth.—The Figure

shows a comparison of the rate of subnormal head circumference (< −2 SDs) among AGA and SGA children at birth and at 40 weeks', 8 months', and 20 months' corrected age. Significantly more SGA infants had a subnormal head circumference at each age measured ($P<.001$). As would be anticipated, only 14 (4%) of the 379 AGA children had a subnormal head circumference at birth. However, 63 (17%) became subnormal at 40 weeks because of poor neonatal growth, and 51 (14%) and 46 (12%), respectively, failed to catch up and remained subnormal at 8 and 20 months of age. In contrast, 54 (53%) of the 102 SGA infants had a subnormal head circumference at birth because of intrauterine growth failure. By 40 weeks some catch-up growth had occurred, with further growth occurring by 8 months. However, 38 (38%) and 25 (25%) infants remained subnormal at 40 weeks and 8 months, respectively. No further catch-up growth occurred thereafter. Twice as many SGA infants had subnormal 8- and 20-month head circumferences compared with the AGA infants.

This cross-sectional presentation of growth failure at each age obscures, however, the varying growth histories among both AGA and SGA children, of whom some demonstrate brain growth failure neonatally, while others demonstrate it after the neonatal period.[1] Thus, in Table 3 we present the varying patterns of growth of the AGA and SGA infants. As can be seen, 14 AGA infants were born with a subnormal head cir-



Percentage of appropriate for gestational age (AGA; n = 379; open bars) and small for gestational age (SGA; n = 102; solid bars) children with a subnormal (< −2 SDs) head circumference at birth, 40 weeks', and 8 and 20 months' corrected age. Significantly more SGA infants had subnormal head circumference at each age ($P<.001$).

Table 3.—Longitudinal Patterns of Brain Growth Failure

Onset of Brain Growth Failure	No. of Infants With Subnormal Head Size by Age			
	Birth	Term	8 mo	20 mo
Appropriate for Gestational Age Infants (n = 379)				
Intrauterine	14	7	5	3
Neonatal		56	23	19
Postneonatal before 8 mo			23	12
Postneonatal after 8 mo				12
Total (%)	**14** (4)	**63** (17)	**51** (14)	**46** (12)
Small for Gestational Age Infants (n = 102)				
Intrauterine	54	28	15	17
Neonatal		10	6	4
Postneonatal before 8 mo			4	3
Postneonatal after 8 mo				2
Total (%)	**54** (53)	**38** (38)	**25** (25)	**26** (26)

Table 4.—Timing of Brain Growth Failure and Neurodevelopmental Outcome at 20 Months of Age*

	Appropriate for Gestational Age (n = 379)			Small for Gestational Age (n = 102)		
	No. of Infants	Mean (± SD) MDI	No. (%) Impaired	No. of Infants	Mean (± SD) MDI	No. (%) Impaired
Normal brain growth throughout	274	96 ± 16	26 (9)	32	91 ± 17	2 (6)
Brain growth failure						
Intrauterine						
Caught up by 40 wk	7	91 ± 12	. . .	24	92 ± 12	2 (8)
Caught up by 8 mo	4	93 ± 14	. . .	15	93 ± 14	1 (7)
No catch up by 8 mo	3	84 ± 25	1 (20)	15	84 ± 25	5 (33)
Neonatal onset						
Caught up by 8 mo	33	93 ± 23	6 (26)	4	104 ± 16	. . .
No catch up by 8 mo	23	72 ± 22	13 (56)	6	84 ± 17	2 (33)
Postneonatal onset						
Before 8 mo	23	78 ± 20	6 (26)	4	76 ± 19	1 (25)
After 8 mo	12	91 ± 25	5 (42)	2	94-(88,100)	. . .

*MDI indicates Bayley Mental Developmental Index.[14]

Table 5.—20-Month Bayley Mental Developmental Index (MDI) by 8-Month Head Circumference

Infants	Mean (±SD) MDI: Normal Head Circumference	Mean (±SD) MDI: Subnormal Head Circumference	F	η^2
Appropriate for gestational age	95.4±17 (n=328)	77.3±21 (n=51)	44.72	.11*
Small for gestational age	92.7±15 (n=77)	82.3±22 (n=25)	6.458	.06†

*<.0001
†<.03.

Table 6.—Regressions of 20-Month Bayley Mental Development Index (MDI) on 8-Month Head Circumference Controlling for Key Biologic and Demographic Factors

Factor*	Unstandardized Regression Coefficient (SE): Appropriate for Gestational Age (n=379)	Unstandardized Regression Coefficient (SE): Small for Gestational Age (n=102)
Neonatal risk score	−0.076†(0.022)	−0.064 (0.045)
Neurologic impairment	−22.097†(2.367)	−22.595†(4.985)
Race	6.819†(1.766)	3.225 (3.311)
Socioeconomic status	−1.720 (0.902)	−4.524†(1.600)
8-mo head circumference	−9.987†(2.416)	−1.040 (3.636)
R^2	.36	.35

*Neonatal risk was measured by Hobel and colleagues'[10] neonatal risk score. Other factors were scored as follows: Neurologic impairment: no impairment, 0; impairment, 1. Socioeconomic status: range from 1 (high) to 5 (low). Race: black, 0; white, 1. Head circumference: normal, 0; subnormal, 1.
†Coefficient exceeds twice its SE ($P<.05$).

cumference that remained subnormal in three infants at 20 months. Additionally, 56 AGA infants had brain growth failure during the neonatal period, although the brain remained small in only 19 of them at 20 months. Of the 54 SGA infants born with a subnormal head circumference, head circumferences remained subnormal in 17 infants at 20 months. Ten of the 48 SGA infants born with a normal head circumference had brain growth failure of neonatal onset. Both AGA and SGA populations also had infants with brain growth failure of postneonatal onset.

Relationship of 20-Month Outcome to Growth Indexes

Table 4 presents the relationship of the timing of brain growth failure and catch-up of growth to the 20-month Bayley MDI score and rate of impairment. Both AGA and SGA infants with brain growth failure of intrauterine, neonatal, or postneonatal onset whose brain growth had caught up by 8 months' corrected age had higher MDI scores and a lower rate of neurosensory impairment than those infants whose brain growth failed to catch up. Brain growth failure that occurred after 8 months of age was minimal and had no effect on the MDI score.

The relationships between the Bayley MDI scores at 20 months' corrected age and normal or subnormal head circumference at 40 weeks' and 8 and 20 months' corrected age was examined further. In AGA infants, a significant association was found between the 20-month MDI score and subnormal head circumference at 40 weeks' and 8 and 20 months' corrected age, whereas among SGA infants the association between the 20-month MDI score and subnormal head circumference began at 8 months' corrected age. The relationship between the 8-month head circumference and the 20-month MDI score was markedly stronger for AGA than for SGA infants (Table 5). Among AGA infants the difference in MDI scores between infants who had a normal vs subnormal head circumference at 8 months was 18.1, whereas the difference among SGA infants was only 10.4. Gestational age at birth had no effect on the MDI score when birth weight was controlled for.

Multivariate Analysis of the Effect of Biologic and Social Factors on 20-Month Outcome

The effect of early brain growth failure on the 20-month MDI score was examined in a multivariate model in which biologic and social variables were controlled for. In a hierarchical multiple regression, the MDI score was regressed on head circumference at 8 months, but only after the neonatal risk score, presence or absence of neurologic impairment, race, and socioeconomic status had been included in the equation. Separate analyses were performed for AGA and SGA infants. The results appear in Table 5.

The most striking finding was that when neonatal risk, neurologic impairment, race, and socioeconomic status were controlled for, the effect of 8-month brain growth failure on the 20-month MDI score differed in AGA and SGA children (Table 6). In AGA children, subnormal head circumference at 8 months had a statistically significant association with the 20-month MDI score; AGA children with postnatal subnormal brain growth whose growth failed to catch up by 8 months scored nearly 10 points lower than AGA children with a normal head circumference at 8 months. In SGA children, a subnormal 8-month head circumference had no significant effect on the 20-month MDI score when other biologic and sociocultural factors were controlled for; the MDI score deficit in SGA children with subnormal 8-month head size compared with those children with a normal 8-month head size was approximately 1 point.

The analysis explains equal proportions of the variance in the 20-month MDI scores in AGA and SGA children (36% and 35%, respectively). In both AGA and SGA children, neurologic impairment is the most important factor and, together with sociocultural indicators, accounts for the major portion of the explained variance in 20-month MDI scores. Of the two sociocultural variables, race predominates in the AGA infants and social class predominates in the SGA children. Neonatal risk has a significant effect on the 20-month MDI score in the AGA children. The failure of neonatal risk to reach statistical significance in the SGA children

is accounted for by the smaller size of the SGA sample.

Differential Causes and Correlates of Subnormal Brain Growth Among AGA and SGA Infants

To explain the differential effect of 8-month head circumference on the 20-month MDI scores of AGA and SGA children, we further examined the association of perinatal events with brain growth failure in AGA and SGA children. We considered pregnancy-induced hypertension, multiple birth, Apgar scores at 1 and 5 minutes, respiratory distress syndrome, and apnea of prematurity. As noted previously, no overt intrauterine infections or brain malformations were diagnosed.

Among the AGA population, the only individual risk factor significantly associated with a subnormal 8-month head size was respiratory distress syndrome ($P<.01$). Among the SGA population, no single risk factor was significantly associated with subnormal 8-month head size. Subnormal head size at 8 months was almost as common in SGA children with a history of respiratory distress syndrome as in those without a history of respiratory distress syndrome (28% [12/43] vs 22% [14/59]). In contrast, subnormal head size at 8 months was far more common in AGA children who had a history of respiratory distress syndrome than in those with no respiratory distress syndrome (17% [43/257] vs 7% [8/122]; $P<.03$). However, among both AGA and SGA children the rate of neurosensory impairment was significantly higher among those who had respiratory distress syndrome compared with those children who did not (19% [49/257] vs 7% [8/122], respectively, for AGA infants [$P<.03$]; 23% [10/43] vs 4% [2/59], respectively, for SGA infants [$P<.005$]). This may be due to the greater risk of anoxic encephalopathy and intraventricular hemorrhage in infants with respiratory distress syndrome.[16]

COMMENT

The results of the present investigation can be summarized as follows: (1) Intrauterine and neonatal risk factors differ between AGA and SGA VLBW infants. (2) Brain growth attainment during infancy, as measured by 8-month head circumference, predicts the 2-year MDI score for both AGA and SGA infants. However, when biologic and social factors are controlled for, subnormal 8-month head circumference does not predict the 20-month MDI score among SGA infants, whereas among the AGA infants it continues to do so.

The predictors of the 20-month MDI score measured in this analysis explain a similar percent of the variance at 20 months' corrected age (35% to 36%). Clearly, the major proportion of the variance remains unexplained. Excluding error variance, such as unreliability of the 20-month MDI score, the major determinants of intelligence, namely genetic transmission and parenting factors, are not considered in this study.

The demographic and perinatal differences between AGA and SGA VLBW infants include the fact that SGA VLBW infants are born at a more advanced gestational age, have a lower birth weight, and are at a slight sociodemographic disadvantage. Their intrauterine growth is impaired mainly by placental insufficiency secondary to pregnancy-induced hypertension, multiple birth, and other, less well-defined causes. Their greater maturity at birth is associated with fewer neonatal complications, including asphyxia, respiratory distress syndrome, and apnea of prematurity.

An examination of the causes of brain growth failure showed that intrauterine causes such as pregnancy-induced hypertension and multiple gestation had a limited effect on outcome in our select population. In contrast, neonatal illness had a devastating influence, as evidenced by the effect of respiratory distress syndrome on neurosensory impairment in both AGA and SGA infants. The fact that repiratory distress syndrome had no effect on head circumference in SGA infants might be explained by the fact that SGA children, even those without respiratory distress syndrome, already had subnormal brain growth that was due to intrauterine causes. The detrimental effect of neonatal illness on growth and developmental outcome has been noted by others.[4,17-21] During the years 1977 through 1982, cerebral ultrasonography was not performed routinely in our unit; however, the contribution of perinatal hypoxic-ischemic injury to outcome can be measured indirectly by the incidence of later neurologic impairment, specifically cerebral palsy. This was more prevalent among AGA children and was probably related to their lower gestational age and higher incidence of asphyxia and respiratory insufficiency, although other causes cannot be excluded.

Based on the above considerations, we suggest that among SGA infants who do not have congenital malformations or intrauterine infections, the effects of intrauterine brain growth failure are different from those of neonatal brain growth failure. Infants with isolated intrauterine brain growth failure who have a benign neonatal course commonly do well or have only slightly depressed MDI scores, whereas those with superimposed neonatal sequelae, such as respiratory distress syndrome, are at greater risk. This might be due to the fact that alteration of brain growth in utero is caused mainly by undernutrition, whereas postnatal undernutrition is confounded by the effects of anoxic encephalopathy. Warshaw[22] has postulated that intrauterine growth failure resulting from a restricted nutrient supply might not represent pathologic disorder but rather might be a favorable adaptation of the fetus to maximize the prospects of good outcome. His postulate is supported by evidence that the stress associated with intrauterine growth failure may accelerate maturity and thus be protective.[23,24] Future utilization of neuroradiologic methods of brain imaging may identify the timing of various components of brain growth and catch-up growth, including gray matter growth and myelinization. Analysis of brains of SGA infants has disclosed biochemical alterations, particularly of the cerebellum. Chase and colleagues[25] have speculated that these deficits might be corrected with optimal postnatal rehabilitation, and Dobbing[26] has stressed the relative importance of postnatal, as compared with intrauterine, growth failure. Our findings of a relative protection from developmental sequelae among SGA infants are consistent with these hypotheses.

In summary, we conclude that in AGA infants subnormal head size at 8 months is an ominous occurrence that

results from major neonatal illness. In contrast, subnormal 8-month head size in SGA infants is of a heterogenous origin, including relatively benign growth retardation in utero as well as superimposed adverse neonatal complications that result in more severe impairment.

Blanche Caron coordinated the study program, and Anne Rivers, PhD, and Susan K. McGrath, PhD, assisted in the collection and analysis of data.

References

1. Hack M, Merkatz IR, Gordon D, et al: The prognostic significance of postnatal growth in very low birthweight infants. *Am J Obstet Gynecol* 1982;143:693-699.

2. Hack M, Breslau N: Very low birth weight infants: Effects of brain growth during infancy on intelligence quotient at 3 years of age. *Pediatrics* 1986;77:196-202.

3. Vohr B, Oh W: Growth and development in preterm infants small for gestational age. *J Pediatr* 1983;103:941-945.

4. Calame A, Ducret S, Jaunin L, Plancherel B: High risk appropriate for gestational age (AGA) and small for gestational age (SGA) preterm infants. *Helv Paediatr Acta* 1983;38:39-50.

5. Koops BL: Neurologic sequelae in infants with intrauterine growth retardation. *J Reprod Med* 1978;21:343-358.

6. Tudhope DI, Burns Y, O'Callaghan M, et al: The relationship between intrauterine and postnatal growth on subsequent psychomotor development of very low birthweight (VLBW) infants. *Aust Paediatr J* 1983;19:3-8.

7. Allen MC: Developmental outcome and follow up of the small for gestational age infant. *Semin Perinatol* 1984;8:123-156.

8. Hack M, Merkatz IR, McGrath SK, et al: Catch-up growth in very-low-birth-weight infants: Potential and clinical correlates. *AJDC* 1984; 138:370-375.

9. Usher R, McLean F: Intrauterine growth of live-born Caucasian infants at sea level: Standards obtained from measurements in seven dimensions of infants born between 25 and 44 weeks of gestation. *J Pediatr* 1969;74:901-910.

10. Hobel C, Hyvarinen M, Okada D: Prenatal and intrapartum high-risk screening: Prediction of the high-risk neonate. *Am J Obstet Gynecol* 1973;117:1-9.

11. Wingerd J, Schoen EJ, Solomon II: Growth standards in the first two years of life based on measurements of white and black children in a prepaid health care program. *Pediatrics* 1971;47: 808-825.

12. Broman SH, Nichols PL, Kennedy WA: *Preschool IQ: Prenatal and Early Developmental Correlates*. Hillsdale, NJ, Lawrence Erlbaum Associates Inc, 1975.

13. Hollingshead AB, Redlich FC: *Social Class and Mental Illness*. New York, John Wiley & Sons, 1958.

14. Bayley N: *Bayley Scales of Infant Development*. New York, The Psychological Corp, 1969.

15. Cohen J, Cohen P: *Applied Multiple Regression of Correlation Analysis for the Behavioral Sciences*, ed 2. Hillsdale, NJ, Lawrence Erlbaum Associates Inc, 1983, p 197.

16. Pape KE, Wigglesworth JS: *Haemorrhage, Ischaemia and the Perinatal Brain*. Philadelphia, JB Lippincott, 1979.

17. Ross G, Lipper EG, Auld AM: Physical growth and developmental outcome in very low birth weight premature infants at 3 years of age. *J Pediatr* 1985;107:284-286.

18. Georgieff MK, Hoffman SJ, Pereira GR, et al: Effect of neonatal caloric deprivation on head growth and one year developmental status in preterm infants. *J Pediatr* 1985;107:581-587.

19. Gross SJ, Oehler JM, Eckerman CO: Head growth and developmental outcome in very low birthweight infants. *Pediatrics* 1983;71:70-75.

20. Villar J, Smeriglio V, Martorell R, et al: Heterogeneous growth and mental development of intrauterine growth-retarded infants during the first three years of life. *Pediatrics* 1984;74:783-791.

21. Commey JOO, Fitzhardinge PM: Handicap in the preterm small-for-gestational age infant. *J Pediatr* 1979;94:779-786.

22. Warshaw JB: Intrauterine growth retardation: Adaptation of pathology? *Pediatrics* 1985;76:998-999.

23. Hadi HA: Fetal cerebral maturation in hypertensive disorders of pregnancy. *Obstet Gynecol* 1984;63:214-219.

24. Gould JB, Gluck L, Kulovich MV: The relationship between accelerated pulmonary maturity and accelerated neurological maturity in certain chronically stressed pregnancies. *Am J Obstet Gynecol* 1977;127:181-186.

25. Chase HP, Welch NN, Dabiere CS: Alterations in human brain biochemistry following intrauterine growth retardation. *Pediatrics* 1972;50:403-411.

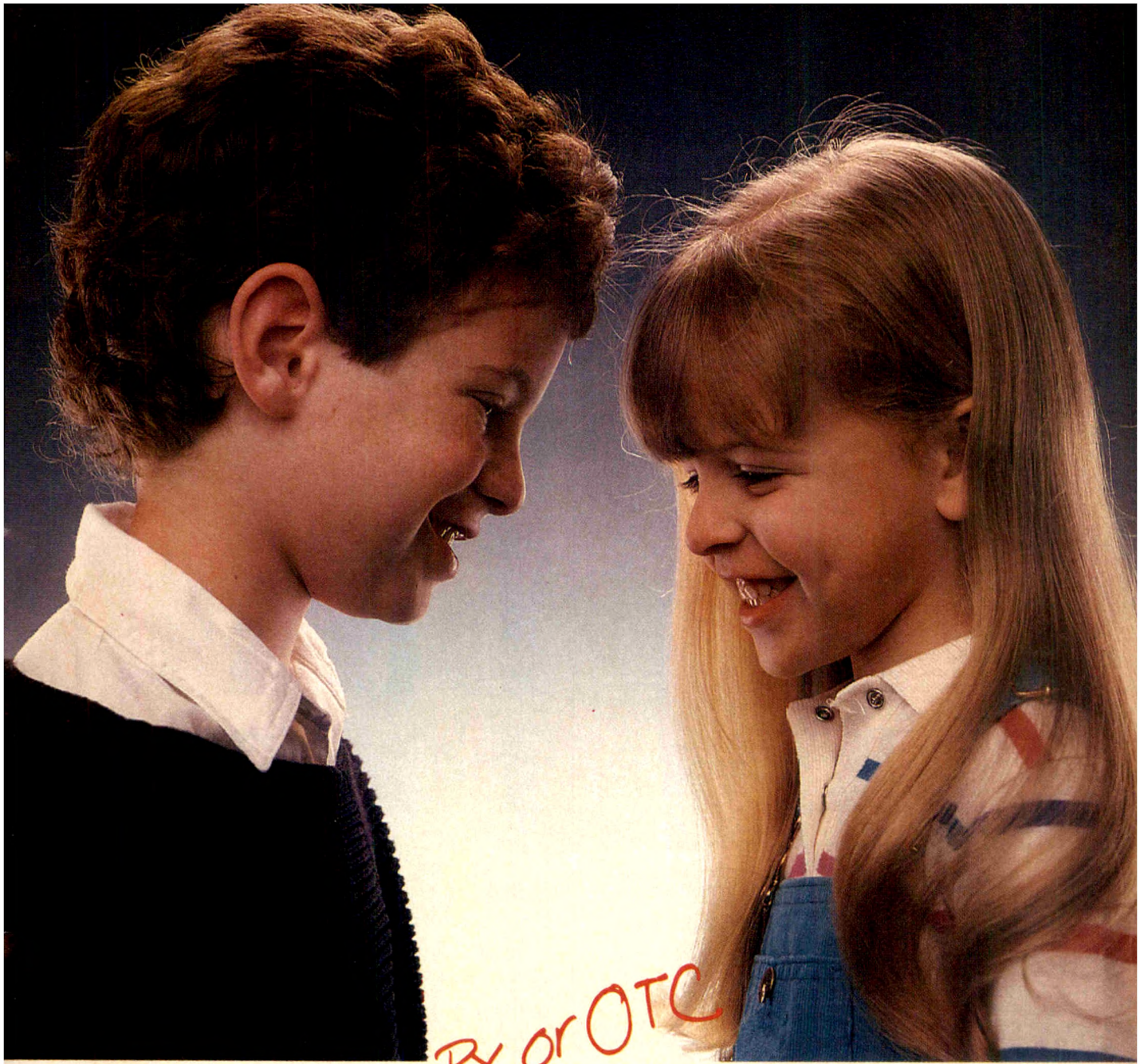
26. Dobbing J: The later development of the brain and its vulnerability, in Davis JA, Dobbing J (eds): *Scientific Foundations of Pediatrics*. Philadelphia, WB Saunders Co, 1974.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Technology Assessment in Medicine: The Role of the American Medical Association

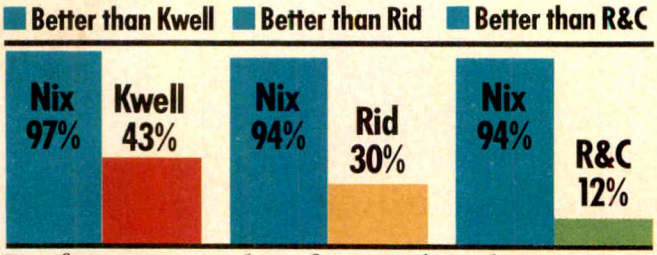
William T. McGivney, PhD, William R. Hendee, PhD (*Arch Pathol Lab Med* 1988;112:1181-1185)



The best treatment Rx or OTC to kill lice and nits

97% effective with one application

Clinical studies prove Nix™ kills lice and nits and protects against reinfestation better than Rid,® Kwell,® or R&C Shampoo.® Only Nix provides 14-day protection against reinfestation–*with one application*–and no evidence of CNS toxicity as reported with lindane overexposure.[1]



Lice-free patients 14 days after a single application.[2,3]
(Rid labelling requires a second application at 7-10 days.)

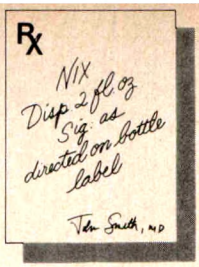
Nix® FOR LICE
CREME RINSE
permethrin 1%

Call 1-800-FOR-LICE
to report head lice outbreaks

Copr. ©1988 Burroughs Wellcome Co. All rights reserved. NI-122
Please see adjacent page for brief summary of prescribing information.

Wellcome

Nix FOR LICE®
CREME RINSE
permethrin 1%



PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovicidal activity against *Pediculus humanus* var. *capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovicidal activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus* var. *capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)

Store at 15°-25°C (59°-77°F).

1. Davies J, Dedhia H, Morgade C, et al: Lindane poisonings, *Arch Dermatol* 1983;119:142-144.
2. Taplin D, Meinking T, Castillero P, et al: Permethrin 1% creme rinse for the treatment of *pediculus humanus* var *capitis* infestation. *Pediatr Dermatol* 1986;3:344-348.
3. Taplin D, Meinking T: Pyrethrins and pyrethroids for the treatment of scabies and pediculosis. *Semin Dermatol* 1987;6:125-135.

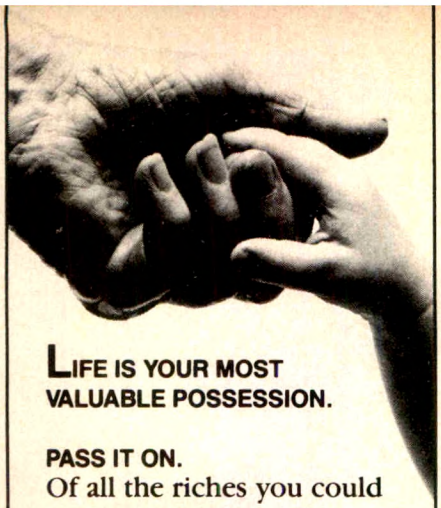
Burroughs Wellcome Co.
3030 Cornwallis Road
Wellcome Research Triangle Park, NC 27709

Don't Forget!

Send for the latest edition of the free Consumer Information Catalog. ☐ The Catalog lists over 200 selected federal publications of consumer interest on subjects like health, nutrition, federal benefits, money management. ☐ The Catalog is free and so are many of the booklets. ☐ Just send your name and address, no strings attached. Write today:

Consumer Information Center
Department DF
Pueblo, Colorado 81009

A public service of this publication and the Consumer Information Center of the U.S. General Services Administration.



LIFE IS YOUR MOST VALUABLE POSSESSION.

PASS IT ON.
Of all the riches you could leave to your family, the most precious is the gift of life. Your bequest to the American Heart Association assures that priceless legacy by supporting research into heart disease prevention.

To learn more about the Planned Giving Program, call us today. It's the first step in making a memory that lasts beyond a lifetime.

WE'RE FIGHTING FOR YOUR LIFE

American Heart Association

This space provided as a public service.

Now, MDI therapy is available to more patients than ever before

New AeroChamber®
WITH *MASK* (aerosol holding chamber)

Permits easier metered-dose-inhaler (MDI) therapy in children and the elderly (see boxed statement below). The device consists of an aerosol holding chamber with a soft, flexible mask that covers the patient's nose and mouth. A one-way valve holds the medication until the patient inhales. Expired air is vented through exhalation ports. AeroChamber with *Mask* is economical and fits virtually any inhaler.

IMPORTANT INFORMATION
Package insert dosing instructions should be consulted for all metered dose inhalers (MDIs) when used with AeroChamber with *Mask*.
Dosage and administration recommendations vary for different MDIs, and the limitations and conditions of use for each product should be considered before utilizing this device, particularly for younger and older patients.

☐ **Yes, I am interested in the New AeroChamber® with *Mask*. Please send more information.** AJDC 1/89

☐ **Enclosed is my check or money order for:**

#Units		Price		Total
_____	×	**$22.00**	=	_____

Minimum order—6 units. Price includes postage and handling.

Name _____ (please print)

Address _____

City _____

State _____ Zip _____

Phone ( ) _____

Clip and mail to: **AeroChamber® with *Mask***
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

For more information or to place an order now, call 1-800-325-1605.

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

© 1988 Forest Pharmaceuticals, Inc. AWM-008-88

Trust is more than a matter of taste.

Trust is knowing that your recommendation stands for efficacy. Dimetapp Elixir has a heritage of efficacy that's unsurpassed for colds and allergy relief. Every spoonful provides effective relief of the runny nose, sniffling and nasal congestion of a cold or flu. Dimetapp Elixir also relieves the itchy, watery eyes and sneezing of little allergy sufferers.

And, Dimetapp is a name that has always stood for great grape taste. So, compliance is never an issue. Trust Dimetapp Elixir. A heritage of efficacy in every good-tasting spoonful.

Dimetapp® Elixir

Nasal Decongestant/Antihistamine

A heritage of efficacy in every spoonful.

© 1989 A.H.Robins Company

The Pediatrician as a Consultant

Gunnar B. Stickler, MD

• **The time has come for pediatricians to assert themselves as consultants. They should be able to take care of most illnesses and children. The pediatrician should decide when help by a subspecialist is needed. The parents should not be expected to be the "brokers" for various specialty services. A tentative list of conditions every pediatrician should be able to handle with confidence is included.**

(*AJDC* 1989;143:73-74)

Subspecialization in medical and surgical fields has brought great advances to pediatrics. Children receive excellent care from medical and surgical subspecialists who see infants and children exclusively. Subspecialists in pediatrics have increased in number, particularly in urban areas, and are, in fact, competing for patients.

However, advances have been followed by disadvantages. Somewhere along the way, some parents have forgotten that a pediatrician is a specialist. Residents in many training programs have become so used to the presence of subspecialists that they find themselves calling for consultations right after the admission of a patient with a complicated case. Residents might even be happier to have children admitted to the services of medical or surgical subspecialists. Whatever triage system is used by the admission system or the emergency department may shunt patients to subspecialists.

For the ambulatory practice, telephone operators, clerks responsible for making appointments, or triage nurses may make the initial decision of who should see patients. The primary physician, a major source of referrals, determines where the patient should be seen. However, with increasing frequency, parents are becoming the "brokers" for the care of their children. Parents decide that a child with joint pain should see an orthopedist and a child who is wetting the bed should be under the care of a pediatric urologist. All these systems can work well. However, they all may have contributed to fractionation of care, overutilization of consultations, and, in some cases, a blurring of focus. Relatively simple problems become magnified, and, in some confusing situations, for instance, a patient with a conversion reaction, this may lead to many unnecessary tests and procedures. The patient's records will bulge and the costs will increase proportionally. Also, diagnoses outside of a subspecialist's area may be missed because they are not considered or inadequately evaluated. Overtesting and subspecialty consultations may result because a certain condition was not recognized clinically.

EXAMPLES OF THE PROBLEM

Some examples should suffice as illustrations of the problem. Admittedly, they are extreme, but they have been observed. A 5-year-old patient with diurnal enuresis is referred to a pediatric urologist. The investigations include a voiding cystourethrogram, an ultrasonographic examination of the kidneys, urodynamic studies, and cystoscopy. Bladder dyssynergia or a "nonneurogenic neurogenic bladder" is suspected, and a pediatric neurologist is consulted. He finds no localizing lesions. Such a patient may well end up receiving oxybutynin chloride. The same patient may come to a pediatrician, who elicits a family history of enuresis, obtains a urine culture that is negative, and suggests a behavior modification program, because the pediatrician knows that there is no difference in the genetic origin of nocturnal enuresis and diurnal enuresis; the latter is just an extension of the former.[1,2]

Another example is of a 2½-year-old girl whose height is below the fifth percentile. In addition to a general physical examination, an endocrinologist will obtain a roentgenogram for bone age; a hematology and chemistry group analysis; thyroxine, thyroid-stimulating hormone, blood, and urine pH studies (because sooner or later somebody is going to ask about renal tubular acidosis); and, last but not least, a consultation with the nutritionist because the patient "does not eat well." She is not given growth hormone, that would be too much in 1988, but perhaps that will happen in 1990. A pediatric consultant would have looked at her growth chart, examined her, and found out that her maternal grandmother measured just 152.5 cm. He would have put the parents' minds at ease and called the patient a beautiful "petite."

These may be caricatures, and these things do not happen in one's own institution, just elsewhere.

A LIST OF CONDITIONS

Some of my colleagues in our community pediatric service and I have put together a tentative list of conditions for which patients may not need to be seen by a subspecialist. The list can easily be expanded, and we do not claim that it is final. It may also serve as a partial list for the American Board of Pediatrics of conditions with which every candidate should be familiar. The examiners on the American Board of Pediatrics recently reaffirmed that they expect a candidate to be a "consultant" or, in other words, to be able to help primary physicians in caring for their pediatric patients.

Accepted for publication Aug 25, 1988.

From the Department of Pediatrics, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Reprints not available.

Children do not necessarily need to see subspecialists if a "consultant" pediatrician is monitoring them for one of the following conditions.

Skin: atopic dermatitis, diaper rash, seborrheic dermatitis, acne, urticaria, tinea, scabies, warts, minor burns, stings and bites, impetigo, hemangioma, and Henoch-Schönlein purpura.

Central nervous system: headaches, migraine, simple seizures with fever, typical grand mal seizures, petit mal seizures, mental retardation, attention deficit hyperactivity disorder, dyslexia, and minor tics.

Behavior: excessive crying in infancy (called "colic"), breath-holding spells, sleep disturbances, school phobia,[3] mild depression, and adjustment disorders.

Ear, nose, and throat and respiratory tract: frequent otitis media, otitis media with chronic effusion, mild hearing defect (conductive) because of effusion, large tonsils, obstructing adenoids, snoring, brief periods of "obstructive" apnea, vasomotor rhinitis, seasonal allergic rhinitis, frequent colds, frequent tonsillitis/pharyngitis, chest pain, pneumonia, and bronchiolitis.

Allergic diseases: adverse food reactions and most cases of asthma.

Heart: innocent murmurs and mild elevation of blood pressure in an obese teenager.

Gastrointestinal tract: spitting up in infants, gastroesophageal reflux, constipation, abdominal pain without any other symptoms, encopresis, and diarrhea.

Genitourinary tract: enuresis (nocturnal and diurnal), recurrent urinary tract infections in girls, vesicoureteral reflex (grade 1, 2, 3), microhematuria, postural proteinuria, and retractile testis.

Musculoskeletal problems: feet turning in or out, flat feet, genu varum, mild scoliosis, torticollis, and sprains.

Endocrine problems: obesity and constitutional short stature.

Hematologic problems: iron deficiency anemia and transient idiopathic thrombocytopenia.

Parasites: pin worms, *Giardia lamblia*, and ascarides.

We as pediatricians should not block consultations, nor should we hold onto the patient if we are not sure about the diagnosis or treatment. However, we should convince primary care physicians about our competence, and we should convince the public of what a pediatrician can handle with ease. Locally, we have to inform our triage systems about what patients pediatricians should see before they are sent to a subspecialist. If a patient is referred from another physician, it is mandatory to communicate and refer the patient back to the primary physician. If we are in danger of losing competence or show signs of weakness in certain areas, we have an obligation to reacquaint ourselves by using the various avenues of postgraduate education open to us. At the same time, we may never have had training in certain areas, such as gynecology, and we should not try to be everything to everybody.

I appreciate the suggestions made by Edward J. O'Connell, MD, Roy F. House, Jr, MD, Patricia S. Simmons, MD, and William A. Smithson, MD.

References

1. Forsythe WI, Redmond A: Enuresis and spontaneous cure rate: Study of 1129 enuretics. *Arch Dis Child* 1974;49:259-263.

2. Burke EC, Stickler GB: Enuresis: Is it being overtreated: *Mayo Clin Proc* 1980;55:118-119.

3. Schmitt BD: School phobia: The great imitator: A pediatrician's viewpoint. *Pediatrics* 1971;48:433-441.

In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Access to Kidney Transplantation

Philip J. Held, PhD; Mark V. Pauly, PhD; Randall R. Bovbjerg, JD; John Newmann, PhD; Oscar Salvatierra, Jr, MD (*Arch Intern Med* 1988;148:2594-2600)

Otologic Manifestations in Congenital Velopharyngeal Insufficiency

Dory G. Durr, MD, FRCSC, Robert S. Shapiro, MD, CM, FRCSC

• A study of ear disease in children with congenital velopharyngeal insufficiency (VPI) was undertaken. A retrospective chart analysis of 80 cases of VPI formed the basis of this review. Thirty-seven percent of the children had evidence of middle ear disease, with middle ear effusion and recurrent otitis media being the most frequent findings. Thirty-one percent had abnormal audiograms, with 20% having a conductive or mixed hearing loss. Overall, 46% of the children had otologic manifestations, indicating the need for the pediatrician and the otolaryngologist together to be actively involved in the evaluation and treatment of this group of children, starting in early infancy.

(*AJDC* 1989;143:75-77)

Velopharyngeal insufficiency (VPI) is the inability of the velopharyngeal sphincter to function effectively during running speech. This results in varying degrees of hypernasality (excessive nasal resonance during phonation) and, in more severe cases, nasal escape (the audible passage of air through an incompetent velopharyngeal sphincter).

Physical examination may reveal an apparently normal palate, a palate that is short or decreased in mobility, or a submucous cleft palate. Submucous cleft palate is identified by the triad of bifid uvula, midline diastasis of the soft palate musculature, and a notch in the posterior margin of the hard palate.

Accepted for publication Sept 9, 1988.

From the Department of Otolaryngology, McGill University and The Montreal Children's Hospital (Drs Durr and Shapiro), and the Cleft Palate Unit (Dr Shapiro), The Montreal Children's Hospital, Montreal. Dr Durr is now in private practice in Yarmouth, Nova Scotia.

Read before the Annual Meeting of the American Society of Pediatric Otolaryngology, Kiawah Island, SC, April 22, 1988.

Reprint requests to 5757 Decelles Ave, Suite 513, Montreal, Quebec H3S 2C3, Canada (Dr Shapiro).

Pruzansky et al[1] classified congenital palatal incompetence (CPI) into two types: type 1 CPIs exhibit one or more of a triad of visible stigmata, including bifid uvula, midline diastasis of the velar musculature, and submucous defect of the hard palate. Type 2 CPIs do not have these stigmata, but have roentgenographic abnormalities that include a short or thin velum, or altered nasopharyngeal dimensions secondary to cervical vertebrae and/or skull anomalies. A broad classification of VPI is presented in Table 1.

Pediatricians should be able to distinguish VPI from other speech disorders. One must be vigilant about avoiding complete adenoidectomy in patients with inadequate palates but without apparent VPI, as the surgery may unmask the VPI. A partial adenoidectomy can often be successfully performed in such a patient.[2]

A high incidence of middle ear problems has been reported in patients with VPI.[3,4] The pediatrician should be aware of this association so that the otologic problems can be anticipated and managed.

PATIENTS AND METHODS

A retrospective chart review of the 80 cases of congenital VPI seen by the senior author (R.S.S.) during a nine-year period (1975 to 1984) was undertaken. There were 42 female patients and 38 male patients. The ages ranged from 3.5 to 23 years, with a mean age of 10.1 years. All patients had the same protocol of investigation, including evaluation by an otolaryngologist, a speech pathologist, a plastic surgeon, and a pediatrician; audiometry; and cine studies of the velopharyngeal mechanism, using barium, in both lateral and basal projections.

Patients were classified into CPI 1, CPI 2, and congenital palatopharyngeal neuromuscular dysfunction (CPND).[5] Patients whose palates were short, but otherwise appeared normal, were classified as CPI 2. The classification of CPND was used to classify patients whose palates appeared normal but had either decreased palatal mobility or decreased lateral pharyngeal wall movement. Adenoidectomy, with or without tonsillectomy, was a precipitating cause of rhinolalia aperta in a number of the cases. It is probable that an underlying congenital problem was present and was unmasked by the adenoidectomy. For this reason, cases of VPI after adenoidectomy, with or without tonsillectomy, were included in the current study. Post-adenoidectomy cases were calculated as a percentage of the whole population of children and of each group. Patients with cleft palate were excluded, as were those whose VPI was post-traumatic or followed palatal resection.

Otologic manifestations were divided into middle ear and inner ear affections. Because there were no other external ear problems, we elected to include the one case of atresia (external and middle ear) into the category of middle ear disease. Middle ear disease was assessed by three means: history of recurrent otitis media, otoscopic examination findings, and audiological findings. Inner ear affection, which basically was represented by sensorineural hearing loss (SNHL), was assessed and documented by audiometry.

Patients who were classified as having middle ear effusion (MEE) had the effusion at the time of the initial otolaryngologic consultation. Patients having recurrent otitis media had at least four documented episodes but without MEE on initial consultation. Those who had both recurrent otitis media and MEE were classified in the MEE group. The presence of conductive hearing loss on audiometry was defined as an air-bone gap averaging 15 dB or greater in the speech frequencies.

RESULTS

Analysis of the whole group (N = 80) was first undertaken. Forty-one (51.25%) of these had a previous history of adenoidectomy with or without tonsillectomy. Thirty (37.5%) of 80 patients had evidence of middle ear disease by

Table 1.—Classification of Velopharyngeal Insufficiency

- Cleft palate
- Congenital palatal incompetence
  - With visible stigmata
  - Without visible stigmata
- Palatopharyngeal neuromuscular dysfunction
  - Congenital
  - Acquired
- Postsurgical
  - Adenoidectomy, tonsillectomy
  - Major resection of palate
- Post-traumatic

Table 2.—Middle Ear Disease (History and/or Examination)*

Finding	No. (%) of Patients
Middle ear effusion	12 (15)
Recurrent otitis media	9 (11.25)
Tympanic membrane perforation	3 (3.75)
Adhesive otitis media	2 (2.5)
Cholesteatoma	2 (2.5)
Stapes fixation	1 (1.25)
Atresia	1 (1.25)
Total	**30 (37.5)**

*Total number of patients was 80.

Table 3.—Abnormal Audiological Findings*

Type of Loss	No. (%) of Patients	
Conductive	11 (13.75)	20%
Mixed	5 (6.25)	
Sensorineural	9 (11.25)	
Total	**25 (31.25)**	

*Total number of patients was 80.

history and/or examination. Table 2 itemizes the types and incidence of middle ear disease. Middle ear effusion and recurrent otitis media were the most common. Twenty-five (31.25%) of 80 patients had abnormal audiograms (Table 3). All of these are included in the group of 30 who had middle ear disease, except for seven of the nine children with SNHL. Sixteen patients (20%) had significant air-bone gaps (conductive and mixed hearing loss); 14 patients (17.5%) had SNHL (mixed and sensorineural). Thus, a total of 37 patients (46.25%) had otologic manifestations.

The patients were divided into the three groups, and the data were analyzed. Fifteen (18.75%) were classified as CPI 1, 50 (62.5%) were classified as CPI 2, and 15 (18.75%) had CPND.

Table 4.—Summary of Results*

	No. (%) of Patients			
	CPI 1	CPI 2	CPND	Total
No. of patients	15 (18.75)	50 (62.5)	15 (18.75)	**80 (100)**
Adenoidectomy with or without tonsillectomy	3 (20)	34 (68)	4 (26.67)	**41 (51.25)**
Middle ear disease	9 (60)	17 (34)	4 (26.67)	**30 (37.5)**
Abnormal audiogram	6 (40)	15 (30)	4 (26.67)	**25 (31.25)**
Total otologic manifestation	9 (60)	22 (44)	6 (40)	**37 (46.25)**

*CPI 1 indicates type 1 congenital palatal incompetence; CPI 2, type 2 CPI; and CPND, congenital palatopharyngeal neuromuscular dysfunction.

In the CPI 1 group, three patients (20%) had a history of adenoidectomy with or without tonsillectomy. Nine (60%) had middle ear disease by means of history and/or otoscopic evaluation. Six (40%) of these had abnormal audiograms (four conductive and two mixed losses). Otologic manifestations were present in nine (60%) of 15 of this group.

In the CPI 2 group, 34 (68%) had a history of adenoidectomy with or without tonsillectomy. Seventeen (34%) had middle ear disease by means of history and/or otoscopic findings. Fifteen (30%) had abnormal audiograms (six conductive, two mixed, seven sensorineural). All except five with pure SNHL had middle ear disease, making otologic manifestations in this group 22 (44%) of 50.

In the CPND group, four (26.67%) had a history of adenoidectomy with or without tonsillectomy. Four (26.67%) had middle ear disease by means of history and/or otoscopic evaluation. Four (26.67%) had abnormal audiograms (one conductive, one mixed, two sensorineural). The two patients with pure SNHL did not have middle ear affections, making otologic manifestations in this group six (40%) of 15. Table 4 summarizes all the results.

These results were analyzed (Table 5). The χ^2 statistic was calculated for the relevant 3×2 table and indicated that the three groups did not differ with respect to middle ear disease and no middle ear disease ($\chi^2 = 4.26$; 2 *df*; $P > .1$). Also, they did not differ with respect to hearing loss and normal hearing ($\chi^2 = 0.72$; 2 *df*; $P > .1$), and, thus, they did not differ significantly with respect to otologic manifestations and lack of otologic manifestations ($\chi^2 = 1.48$; 2 *df*; $P > .1$). There was a statistically significant difference in patients who had adenoidectomy, with or without tonsillectomy, and those who did not, in the three groups ($\chi^2 = 15.12$; 2 *df*; $P < .005$). The CPI 2 group had a high incidence (68%) of patients who had adenoidectomy, with or without tonsillectomy, where the VPI was unmasked by surgery. The incidence of adenoidectomy in CPI 1 and CPND was only 20% and 26.67%, respectively.

Table 5.—Statistical Analysis

	χ^2(2*df*)	*P*
Middle ear disease	4.26	>.1
Abnormal audiogram	0.72	>.1
Total otologic manifestation	1.48	>.1
Adenoidectomy ± tonsillectomy	15.12	<.005

COMMENT

The otologic manifestations of cleft palate are well recognized. A study by Stool and Randall[6] revealed middle ear disease in 93% of patients with cleft palate. The incidence of otopathology has also been studied in submucous cleft palate and bifid uvula. In 58 cases of submucous cleft palate studied by Bergstrom and Hemenway,[7] 39.6% were found to have middle ear disease. In bifid uvula, incidences of otologic

abnormalities of 36.5% to 73% were reported.[8,9] These studies, however, did not indicate if these velar anomalies were associated with rhinolalia aperta (VPI).

Two studies reported the incidence of ear disease in patients with VPI. Heller et al[3] studied 77 patients with VPI: 17 with submucous cleft palate, 17 with palatal paresis, and 43 with palatopharyngeal disproportion. They reported a 44% incidence of abnormalities of the tympanic membrane; 39% had significant air-bone gaps. Caldarelli[4] reported 95 cases. He divided his patients into CPI 1 and CPI 2. Abnormal otoscopic findings were found in 50% of CPI 1 cases and 42% of CPI 2 cases. An abnormal audiogram was found in 67% of CPI 1 cases and 74% of CPI 2 cases.

The incidence of SNHL found in this study, and reported by others,[3,7] remains an observation for further confirmation and explanation.

The high incidence (68%) of patients in the CPI 2 group who had adenoidectomy, with or without tonsillectomy, where the VPI was unmasked by the surgery, was strikingly higher than the 20% and 26.67% incidences of adenoidectomy in CPI 1 and CPND groups, respectively. This may indicate that in some patients with CPI 1 and CPND, adenoidectomy was avoided because the otolaryngologist was cautioned by the presence of visible stigmata on physical examination.

Middle ear disease was found in 37.5% of the patients and a significant air-bone gap in 20% (all of them with middle ear disease). There was a higher incidence of middle ear disease in the CPI 1 group compared with the other groups (although it was not statistically significant because of the small groups involved). It may be that the palatal abnormality in the CPI 1 group is closer to overt cleft palate.

Our impression that middle ear disease was less frequent in our patients than what had previously been reported was what initially led us to review our cases. In fact, we found less middle ear disease and significant air-bone gaps than was previously reported, but the incidence was much higher than in the normal population. Middle ear disease in congenital VPI is probably related to anatomic/physiologic dysfunction of the eustachian tube, similar to what is observed in patients with a cleft palate, but to a lesser degree.

CONCLUSIONS

A high incidence of ear disease was found in children with congenital VPI. The pediatrician and the otolaryngologist must be actively involved in the evaluation and treatment of this group of children, starting in early infancy. A persistent middle ear effusion in an infant should alert the pediatrician to the possibility of the presence of a submucous cleft palate.

The authors gratefully acknowledge the editorial assistance of Mary B. Cardozo, MA, Speech Pathology Department, The Montreal Children's Hospital.

References

1. Pruzansky S, Peterson-Falzone S, Laffer J, et al: Hypernasality in the absence of an overt cleft: Commentary on nomenclature, diagnosis, classification and research design, abstract 60. Read before the Third International Congress on Cleft Palate and Related Craniofacial Anomalies, Toronto, June 7, 1977.

2. Shapiro RS: Partial adenoidectomy. *Laryngoscope* 1982;92:135-139.

3. Heller JC, Gens GW, Croft CB, et al: Conductive hearing loss in patients with velopharyngeal insufficiency. *Cleft Palate J* 1978;15:246-253.

4. Caldarelli DD: Incidence and type of otopathology associated with congenital palatopharyngeal incompetence. *Laryngoscope* 1978;88:1970-1984.

5. Cotton R, Nuwayhid NS: Velopharyngeal insufficiency, in Bluestone CD, Stool SE (eds): *Pediatric Otolaryngology.* Philadelphia, WB Saunders Co, 1983, pp 1521-1542.

6. Stool SE, Randall P: Unexpected ear disease in infants with cleft palate. *Cleft Palate J* 1967; 4:99-103.

7. Bergstrom L, Hemenway WG: Otologic problems in submucous cleft palate. *South Med J* 1971;64:1172-1177.

8. Saad EF: The bifid uvula in ear, nose and throat practice. *Laryngoscope* 1975;85:734-737.

9. Taylor GD: The bifid uvula. *Laryngoscope* 1972;82:771-778.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

The Impact of New Features of Laboratory Information Systems on Quality Assurance in Anatomic Pathology

Bruce A. Friedman, MD (*Arch Pathol Lab Med* 1988;112:1189-1191)

Pulmonary Function in Preterm Infants Following Treatment With Intravenous Indomethacin

Alfred N. Krauss, MD; Nunzia Fatica, MD; Barbara S. Lewis, MD; Rebecca Cooper, MD; Howard T. Thaler, PhD; Constance Cirrincione, MS; John O'Loughlin, MD; Aaron Levin, MD; Mary Allen Engle, MD; Peter A. M. Auld, MD

• Pulmonary function tests, including measurements of arterial blood gas levels, total pulmonary compliance, and arterial-alveolar oxygen ratios, were performed in 38 ventilator-dependent preterm infants with respiratory distress syndrome who weighed less than 1500 g at birth. Twenty-seven had a physiologically significant patent ductus arteriosus (PDA). Twelve were assigned at random to receive three doses of intravenous indomethacin, 0.2 mg/kg per dose, on the fourth day of life. This treatment resulted in ductal closure in seven infants by the seventh day of life. Another concurrently observed group of 15 infants with PDA received no indomethacin. A third group of 11 infants lacked evidence of a PDA. Pulmonary function in the infants who received indomethacin did not differ significantly from that in the other two groups.

(*AJDC* 1989;143:78-81)

A physiologically significant patent ductus arteriosus (PDA) frequently occurs in preterm infants with hyaline membrane disease.[1-3] Because of the association between a PDA and a decrease in pulmonary compliance,[4-8] closure of the PDA by either surgical or medical means has been advocated.[8-10] Indomethacin is commonly administered during the first week of life to obtain ductal closure in preterm infants with hyaline membrane disease. Several reports have indicated a beneficial effect on lung function following ductal closure in older infants with respiratory distress or with a PDA that presents as congenital heart disease. The present study in preterm infants receiving ventilatory support was undertaken to measure the effects of a PDA on pulmonary function and to determine the changes in pulmonary function following intravenous administration of indomethacin.

Accepted for publication June 20, 1988.

From the Perinatology Center (Drs Krauss, Cooper, and Auld and Ms Lewis) and the Division of Pediatric Cardiology (Drs Fatica, O'Loughlin, Levin, and Engle), Cornell University Medical College, and the Biostatistics Laboratory, Memorial Hospital–Sloan Kettering Laboratory (Dr Thaler and Ms Cirrincione), New York.

Reprint requests to New York Hospital, 1300 York Ave, New York, NY (Dr Krauss).

SUBJECTS AND METHODS

Subjects

The subjects of this study were 38 preterm infants with hyaline membrane disease, all of whom weighed less than 1500 g at birth, who were ventilator-dependent at 24 hours of age. All infants were studied with their parents' knowledge and consent, obtained under a protocol approved by the local institutional review board. All infants who were ventilator-dependent at 24 hours of age were considered eligible for this study unless they had one or more of the following exclusion criteria: serum creatinine level greater than 110 μmol/L, serum urea nitrogen level greater than 10.5 mmol/L, platelet count less than 60×10^9/L, urinary output less than 0.6 mL/kg/h over the eight hours preceding evaluation, laboratory evidence of infection or of active bleeding, necrotizing enterocolitis, severe (grade 4) intraventricular hemorrhage, congenital anomalies, or lack of parental consent.

On admission to the neonatal intensive care unit, usually within three hours of birth, all infants who weighed less than 1500 g were examined by a neonatologist and a pediatric cardiologist to evaluate their cardiopulmonary status. The infants were reevaluated daily throughout the study period of seven days.

Methods

With respect to the patency of the ductus arteriosus, 27 subjects had evidence of a PDA and 11 did not on clinical and echocardiographic examination. Those with a PDA were assigned by random number to one of two treatment groups. Infants in group 1 received three doses of 0.2 mg/kg of indomethacin intravenously between 72 and 96 hours of age. No infants were retreated. Group 2 infants did not receive indomethacin. Infants who lacked clinical evidence of a PDA were assigned to group 3. No infants had evidence of congestive heart failure during the first week of life.

All infants were treated identically in all other respects. The ventilators of all patients were adjusted to maintain an arterial pH between 7.3 and 7.5. Arterial oxygen tension was maintained between 40 and 70 mm Hg. During the first 24 hours of life, all infants received 80 mL/kg of intravenous fluids. This rate was then adjusted according to the patient's clinical condition.

Pulmonary function studies included determination of arterial carbon dioxide pressure (Pco_2), arterial oxygen pressure (Po_2), pH, total pulmonary compliance, respiratory rate, and measurement of inspired oxygen concentration (Fio_2). The ratio of arterial to alveolar oxygen tension ($a\text{-}Ao_2$) was calculated based on these determinations.[11] These studies were made at 24 hours, 3 days, 5 days, and 7 days of age. Arterial blood gas concentrations and pH were determined immediately after blood sampling on a blood gas analyzer (No. 513, Instrumentation Laboratories, Boston) that was calibrated daily. Pulmonary compliance was determined by placing a water-filled catheter in the subject's esophagus. The catheter was attached to a transducer (No. P23db, Statham Corp, Hato Rey, Puerto Rico) that was calibrated against a water manometer and attached to a carrier amplifier (No. 8812, Hewlett-Packard Corp, Waltham, Mass). The location of the catheter was established by identifying cardiac pulsations on the pressure tracing obtained from the amplifier in conjunction with maximal excursions in phase with the patient's breathing. The tidal volume was simultaneously measured with a pneumotachograph mask with a dead space of less than 2 mL placed between the patient's endotracheal tube and the respirator circuit. The pneumotachograph had a resistance of 1 cm $H_2O/L \times s^{-1}$. Pressures from the pneumotachograph were measured with a transducer (No. 270, Hewlett-Packard Corp) and displayed on a recorder (No. 7700, Hewlett-Packard Corp) at a paper speed of 25 mm/s. The pneumotachograph signals were electronically integrated by means of a respiratory integrator (No. 8815, Hewlett-Packard Corp). The pneumotachograph was calibrated by injecting known volumes from a syringe, and the response was linear throughout the range of tidal volumes encountered in this study.

In addition to a daily physical examination, cardiologic evaluation included an electrocardiogram, a two-dimensional echocardiogram, and a pulsed Doppler echocardiogram. The two-dimensional echocardiogram was performed with a mechanical sector scanner (Mk 300 or Mk 600, Advanced Technology Laboratories, Bellevue, Mass). The studies were performed using the 5.0 MHz short-

focus crystal and were recorded on videotape. Long-axis, short-axis, subxiphoid, apical–four-chamber, and suprasternal views were obtained in each study.

The ratio of the diameters of the left atrium and aortic root (LA/Ao) was calculated in the long-axis view. With the short-axis view the patency of the ductus arteriosus was confirmed, whenever possible, by direct visualization or by contrast injection of normal saline into an umbilical artery catheter with its distal end in the high thoracic aorta. The subxiphoid–four-chamber view was useful to evaluate the size of the left atrium and to see if bulging of the atrial septum into the right atrium was present, as occurs in the presence of a significant left-to-right shunt at the ductal level. All ductal flow was left to right. Two-dimensional echocardiography was also used to exclude other congenital cardiac lesions.

Pulsed Doppler echocardiography was performed with a mechanized sector scanner (Mk 600). Two studies were performed with the same short-focus crystal used for two-dimensional echocardiography and were recorded on videotape. The sampled volume included the main pulmonary artery and the aortic end of the ductus arteriosus. Continuous flow was considered suggestive of a PDA. All echocardiographic examinations were reviewed by a second cardiologist who was unaware of the patient's physical findings or treatment group, and agreement was reached concerning the interpretation of the echocardiogram.

Analysis of Data

To assess statistical significance, recorded data were analyzed using Student's *t* tests, both paired and unpaired, as appropriate, and analysis of variance.[12,13] Transformations were applied to the data, as appropriate, to normalize skewed distributions. Group mean values are reported along with their SEMs to facilitate comparisons of central values between groups. An evaluation of statistical power, namely, the ability of the test to have an 80% likelihood of detecting a statistically significant change at the .05 level, was carried out.[14] These results are presented in Table 1. An adequate sample size required to achieve this likelihood ranged from 20 patients needed to detect a significant change in a-Ao_2 from 0.32 to 0.50 to a sample size of four needed to detect a doubling of compliance from 1.0 mL/cm of water to 2.0 mL/cm of water. Because of the large SD observed in the duration of oxygen therapy, the sample was inadequate to detect a reduction in the duration of oxygen treatment from 40 days to either 32 days (312 patients needed) or 20 days (35 patients needed). Due to the number of multiple statistical tests performed, a more stringent requirement than $P<.05$ should be used to determine statistical signif-

Table 1.—Power of Statistical Tests

Measurement	Sample Size Needed for $\alpha = .05$	Power by Group		
		1 (n=12)	2 (n=15)	3 (n=11)
a-Ao_2*	20	0.60	0.68	0.55
Total pulmonary compliance, mL/cm H_2O	4	0.99	0.99	0.99
% O_2 in inspired air	13	0.75	0.84	0.70
LA/Ao†	6	0.97	0.99	0.96
No. of days receiving O_2 therapy	312	<0.50	<0.50	<0.50

*Ratio of arterial to alveolar oxygen tension.
†Ratio of diameters of left atrium and aortic root.

Table 2.—Data of Study Infants*

Measurement	Group†	Day 1	Day 3	Day 5	Day 7
Weight, g	1	1183±77	1169±75	1151±75	1190±73
	2	1022±58	996±65	930±60	930±60
	3	1233±78	1154±74	1119±77	1102±68
pH	1	7.35±.02	7.36±.01	7.34±.03	7.33±.01
	2	7.37±.02	7.33±.03	7.35±.02	7.37±.02
	3	7.37±.02	7.39±.02	7.34±.01	7.36±.02
CO_2 pressure, mm Hg	1	37±2	38±2	47±7	41±2
	2	33±2	39±4	40±2	43±2
	3	36±2	32±2	39±1	37±2
O_2 pressure, mm Hg	1	62±6	80±10	70±6	66±8
	2	78±10	63±4	61±4	59±4
	3	63±5	54±7	78±6	71±10
a-Ao_2§	1	0.22±0.03	0.38±0.06	0.45±0.06	0.47±0.05
	2	0.34±0.05	0.40±0.05	0.45±0.04	0.46±0.04
	3	0.29±0.03	0.32±0.07	0.58±0.04	0.53±0.09
Total pulmonary compliance, mL/cm H_2O	1	1.86±0.53	1.72±0.68	1.83±0.95	0.89±0.16
	2	1.06±0.22	1.02±0.14	0.75±0.10	0.84±0.12
	3	1.23±0.42	1.15±0.22	1.28±0.17	1.03±0.21
% O_2 in inspired air‖	1	52±6	38±5	34±6	30±6
	2	43±5	36±6	25±1	25±2
	3	39±3	33±3	24±1	25±2
LA/Ao¶	1	1.7±0.1		1.5±0.1	
	2	1.4±0.1		1.4±0.1	
	3	1.3±0.1		1.3±0.1	

*Values are mean±SEM.
†For group 1 (patent ductus arteriosus [PDA], intravenous indomethacin), n=12 on days 1, 3, and 5, and n=11 on day 7. For group 2 (PDA, no indomethacin), n=15 on days 1 and 3, n=14 on day 5, and n=13 on day 7. For group 3 (no evidence of PDA), n=11 on days 1 and 3, and n=10 on days 5 and 7.
‡$P<.05$ compared with group 2 on day 1.
§Ratio of arterial to alveolar oxygen tension.
‖For group 1, duration of O_2 treatment was 40±8 days (range, six to 88 days); group 2, 53±10 days (range, four to 129 days); and group 3, 32±13 days (range, five to 146 days).
¶Ratio of diameters of left atrium and aortic root.

icance (eg, $P<.005$), and borderline results (eg, $.005<P<.05$) should be regarded as suggestive of trends.

RESULTS

Effects on Pulmonary Function and Ductal Closure

Statistical data are presented in Tables 2 and 3. With the exception of a lower weight in group 2 patients on the seventh day of life, no statistically significant differences in clinical condition or pulmonary function were found among patients in any of the three groups during the first week of life. All surviving patients tended to improve during the first week of life. Comparison of data failed to indicate any significant differences among the three groups in the rate or degree of improvement. Infants with a PDA who did not receive indomethacin required supplemental oxygen for the greatest duration (53 ± 10 days), while infants who lacked clinical evidence of a PDA had the shortest average duration for supplemental oxygen (32 ± 13 days). However, these differences were not statistically significant.

Patients with clinical and/or laboratory evidence of a PDA (groups 1 and 2) were analyzed according to whether or not the ductus arteriosus remained patent on days 5 and 7 of life. The PDA closed by day 7 in seven (58%) of 12 infants in group 1 who received indomethacin and in two (13%) of 15 infants in group 2 who did not. On day 5, infants whose ductus closed after indomethacin had a significantly higher a-AO_2 ratio (0.58 ± 0.18) than infants in group 1 who did not respond to indomethacin (0.26 ± 0.11, $P<.05$). Infants in group 2 whose PDAs closed spontaneously showed no other statistically significant differences compared with both control and indomethacin-treated infants. Infants who received indomethacin but whose ductus remained patent also had a significantly lower a-AO_2 ratio than infants with a PDA who did not receive indomethacin (0.26 ± 0.11 vs 0.46 ± 0.15, $P<.05$). Infants whose ductus remained patent after indomethacin also had a significantly greater oxygen requirement (FiO_2) on day 5 than infants who had a PDA but did not receive indomethacin (0.50 ± 0.34 vs 0.25 ± 0.05, $P<.05$).

On the seventh day of life, infants who responded to indomethacin had a significantly lower FiO_2 than infants whose ductus arteriosus closed spontaneously (0.22 ± 0.02 vs 0.29 ± 0.08, $P<.05$). No other statistically significant differences were found.

Table 3.—Paired *t*- Test Data of Study Infants*

Measurement†	Group	Paired *t* Test: Day 3 vs Day 5	Paired *t* Test: Day 3 vs Day 7
pH	1	0.02 ± 0.02	0.03 ± 0.02
	2	−0.02 ± 0.02	−0.04 ± 0.03
	3	0.06 ± 0.027‡	0.02 ± 0.02
CO_2 pressure, mm Hg	1	−9 ± 7	−3 ± 3
	2	−4 ± 1§	−7 ± 2‖
	3	−8 ± 3¶	−5 ± 2
O_2 pressure, mm Hg	1	10 ± 9	14 ± 6#
	2	4 ± 6	6 ± 6
	3	−27 ± 6**	−13 ± 10
a-Ao_2††	1	−0.07 ± 0.10	−0.09 ± 0.08
	2	0 ± 0.05	−0.01 ± 0.07**
	3	−0.25 ± 0.09‡‡	−0.16 ± 0.04
Total pulmonary compliance, mL/cm H_2O	1	−0.11 ± 0.38	0.95 ± 0.69
	2	0.18 ± 0.16	0.13 ± 0.14
	3	−0.32 ± 0.20	−0.12 ± 0.21
% O_2 in inspired air	1	4 ± 5	8 ± 6
	2	3 ± 3	3 ± 4
	3	7 ± 3§§	7 ± 2**

*Values are mean ± SEM.
†For ratio of diameters of left atrium and aortic root before vs after treatment with indomethacin, for group 1, $t = 0.2 \pm 0.1$; group 2, $t = -0.1 \pm 0.13$; and group 3, $t = 0.1 \pm 0.1$.
‡$P = .03$ compared with day 3.
§$P = .017$ compared with day 3.
‖$P = .004$ compared with day 3.
¶$P = .039$ compared with day 3.
#$P = .028$ compared with day 3.
**$P = .003$ compared with day 3.
††Ratio of arterial to alveolar oxygen tension.
‡‡$P = .019$ compared with day 3.
§§$P = .029$ compared with day 3.

Morbidity and Mortality

No infant participating in this study experienced any complications either as a result of the study procedures or as a result of treatment with intravenous indomethacin. One patient in group 1 who received intravenous indomethacin died of progressive pulmonary failure within 48 hours after receiving the drug, and two others died after completion of the study, both of respiratory failure. One infant in this group underwent surgical ligation of the ductus arteriosus successfully after completion of the study. In group 2, two infants with clinically significant PDA who did not receive intravenous indomethacin died on the fifth and seventh days of life, respectively, due to progressive hyaline membrane disease. An additional infant in this group died of overwhelming infection after completion of this study. In group 3, one infant with no clinical evidence of a PDA died on the fourth day of life of progressive respiratory failure. No infant in group 3 required later medical or surgical treatment.

COMMENT

When infants whose PDAs closed either spontaneously or following indomethacin therapy were compared with those who continued to demonstrate evidence of ductal patency, few significant statistical differences were found. These findings suggest that in infants with hyaline membrane disease who did not have cardiac failure, the presence of

a PDA had little effect on pulmonary function during the first week of life. Furthermore, we found that treatment with indomethacin had little effect on pulmonary function per se but did have an effect on closure of the ductus arteriosus.

The power of our statistical tests is indicated in Table 3. The groups, though small, permitted at least an 80% chance of detecting statistically significant changes in pulmonary function between the groups. The only exception concerned the duration of oxygen therapy. Two groups of infants have been the subjects of pulmonary function studies in relation to the presence of a PDA: children with cardiac disease[4-7] and infants with neonatal respiratory distress.[8-10] Most investigators are in agreement that children with congenital heart disease and a PDA have reduced pulmonary compliance.[4-7] However, studies have failed to reveal any clear correlation between reduced pulmonary compliance and increased pulmonary blood flow,[7] although the study of Howlett[6] indicated a correlation between roentgenographic evidence of pulmonary vascular congestion and reduced pulmonary compliance. None of the studies of children with congenital heart disease included infants with pulmonary disease, and most studies included a variety of cardiac diagnoses.

In previously published studies of infants with hyaline membrane disease, both Gerhardt and Bancalari[8] and Naulty et al[9] reported improved pulmonary compliance in infants who underwent surgical ligation of a ductus arteriosus. Medical treatment of the ductus arteriosus has not been associated with the same improvement as surgical therapy.[3,4] Several factors may account for this: (1) Only 50% to 80% of infants achieve ductal closure in the first 48 hours following indomethacin therapy.[3] Infants who fail to undergo ductal closure cannot be expected to demonstrate any favorable effects on pulmonary function other than those to be expected from the ordinary course of recovery. (2) The contribution of the PDA to the clinical severity of hyaline membrane disease may be variable. Jacob et al[15] found that infants with early appearance of significant left-to-right shunting had more severe disease than infants without ductal shunting. The influence of a PDA on pulmonary function in infants with hyaline membrane disease has recently been questioned by the data of Clyman et al.[16] In a group of preterm lambs with respiratory distress studied by these investigators, no significant changes in dynamic compliance were found within 40 minutes of opening a duct with a flow of up to 70% of left-ventricular output.

To date, only Yeh et al[10] have studied pulmonary function in infants with hyaline membrane disease in relation to indomethacin treatment of a PDA. They demonstrated improved compliance in a small group of infants who received intravenous indomethacin on the seventh day of life compared with placebo-treated controls. The infants in this study did not require assisted ventilation, indicating that these infants were less severely ill than those included in our study. They were also treated with intravenous indomethacin later, at a mean postnatal age of 7.1 days. Thus, the results of Yeh et al are not directly comparable to ours. Other studies claiming a beneficial effect on pulmonary function base this claim on improved survival, reduced oxygen requirements, or a reduced duration of oxygen therapy.[3,17-20] The results of the present study are similar to those of Mahony et al,[20] who were unable to demonstrate statistically significant differences in the duration of oxygen therapy and the duration of endotracheal intubation when infants who received intravenous indomethacin on the second day of life were compared with a similar group of placebo-treated infants. Measures of pulmonary function, such as compliance or a-AO_2, were not reported.[20]

Intravenous indomethacin did not have any significant effects on the speed of recovery during the first week of life in infants in the present study. Successful closure of a PDA with intravenous indomethacin did not appear to exert any significant effect on the rate of recovery of pulmonary function during the time period in the present investigation.

Intravenous indomethacin should not be used routinely in preterm infants with hyaline membrane disease but should be reserved for those infants who exhibit poor clinical progress when a PDA complicates neonatal respiratory distress.

References

1. Kitterman JA, Edmunds H, Gregory GA, et al: Patent ductus arteriosus in premature infants. *N Engl J Med* 1972;287:473-477.
2. Siassi B, Blanco C, Cabal LA, et al: Incidence and clinical features of patent ductus arteriosus in low-birthweight infants: A prospective analysis of 150 consecutively born infants. *Pediatrics* 1976; 57:347-351.
3. Gersony WM, Peckham GJ, Ellison RC, et al: Effects of indomethacin in premature infants with patent ductus arteriosus: Results of a national collaborative study. *Pediatrics* 1983;102:895-906.
4. Wallgren G, Geubelle F, Koch G: Studies of the mechanics of breathing in children with congenital heart disease. *Acta Paediatr Scand* 1960; 49:415-425.
5. Griffin AJ, Ferrara JD, Lax JO, et al: Pulmonary compliance: An index of cardiovascular status in infancy. *AJDC* 1972;123:89-95.
6. Howlett G: Lung mechanics in normal infants and infants with congenital heart disease. *Arch Dis Child* 1972;47:707-715.
7. Bancalari E, Jesse MJ, Gelband H, et al: Lung mechanics in congenital heart disease with increased and decreased pulmonary blood flow. *J Pediatr* 1977;90:192-195.
8. Gerhardt T, Bancalari E: Lung compliance in newborns with patent ductus arteriosus before and after surgical ligation. *Biol Neonate* 1980;38: 96-105.
9. Naulty CM, Horu S, Coury J, et al: Improved lung compliance after ligation of patent ductus arteriosus in hyaline membrane disease. *J Pediatr* 1978;93:682-684.
10. Yeh TF, Tholji A, Lukens L, et al: Improved lung compliance following indomethacin therapy in premature infants with persistent patent ductus arteriosus. *Chest* 1981;80:689-700.
11. Gilbert R, Keighley JF: The arterial/alveolar oxygen tension ratio: An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis* 1974;109:142-145.
12. Zar JH: *Biostatistical Analysis.* Englewood Cliffs, NJ, Prentice-Hall International Inc, 1974.
13. Daniel WW: *Biostatistics: A Foundation for Analysis in the Health Sciences*, ed 3. New York, John Wiley & Sons Inc, 1983.
14. Cohen J: *Statistical Power Analysis for the Behavioral Sciences.* Orlando, Fla, Academic Press Inc, 1977.
15. Jacob J, Gluck L, DiSessa T, et al: The contribution of PDA in the neonate with severe RDS. *J Pediatr* 1980;96:79-87.
16. Clyman RI, Mauray F, Heymann MA, et al: Cardiovascular effects of patent ductus arteriosus in preterm lambs with respiratory distress. *J Pediatr* 1987;111:579-587.
17. Yeh TF, Luken JA, Thalji A, et al: Intravenous indomethacin therapy in premature infants with persistent ductus arteriosus: A double-blind controlled study. *J Pediatr* 1981;98:137-145.
18. Merritt TA, Harris JP, Roghmann K, et al: Early closure of the patent ductus arteriosus in very low-birth-weight infants: A controlled trial. *J Pediatr* 1981;99:281-286.
19. Mahony L, Carnero V, Brett C, et al: Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birth-weight infants. *N Engl J Med* 1982;306:506-510.
20. Mahony L, Caldwell RL, Girod DA, et al: Indomethacin therapy on the first day of life in infants with very low birth weight. *J Pediatr* 1985;106:801-805.

Changes in Nutritional Management and Outcome of Very-Low-Birth-Weight Infants

Michael K. Georgieff, MD; Marla M. Mills, RN; Linda Lindeke, PNP; Sandra Iverson, PNP; Dana E. Johnson, MD, PhD; Theodore R. Thompson, MD

• We compared the in-hospital and postdischarge growth of 47 preterm very-low-birth-weight infants born in 1982 with that of 29 born in 1986. Infants in the two groups were of comparable gestational age, size, and illness at birth. During hospitalization, the 1986 infants began parenteral and enteral nutrition earlier, had fewer days when they received less than 252 kJ/kg, were treated earlier for patent ductus arteriosus (6.1 ± 4.5 days vs 14.5 ± 7.7 days), and had a lower prevalence of severe medical complications. By hospital discharge, these infants had significantly higher mean growth percentiles and fewer of them had weights and occipitofrontal circumferences below the fifth percentile. Follow-up at 4 and 12 months corrected age showed that these infants continued to have significantly higher growth percentiles, and fewer of them had weights below the fifth percentile (49% vs 24%) or major neurologic abnormalities. Infants whose weights were below the fifth percentile had significantly poorer 12-month developmental outcomes. We speculate that more aggressive early neonatal nutritional management, changes in cardiopulmonary management, and lower incidences of chronic disease promote earlier onset of and more rapid rates of postnatal growth, which extend through the first year of follow-up.

(*AJDC* 1989;143:82-85)

Advances in neonatal medicine have resulted in improved survival rates and developmental outcomes for premature infants, particularly for those with birth weights less than 1500 g.[1] These changes in outcome have been largely attributed to a better understanding and management of neonatal pulmonary, fluid, and nutritional pathophysiology. In spite of the improved developmental outcome seen during the past several years, no recent studies have assessed whether a concomitant improvement has occurred in the nutritional outcome of these infants. Several investigators have demonstrated the prognostic effect of both intrauterine and extrauterine growth failure on developmental outcome of premature infants, implying that an important link exists between neonatal nutritional status, brain growth, and development.[2-6]

This study compares the nutritional and short-term neurodevelopmental outcomes of preterm very-low-birth-weight (VLBW) infants hospitalized in 1986 with those of similar infants hospitalized in 1982, and documents differences in nutritional and medical managements as well as the prevalence of chronic diseases that may affect growth and nutritional outcome.

PATIENTS AND METHODS

The study group consisted of all 76 premature infants appropriate for gestational age with birth weights less than 1500 g admitted to the Newborn Intensive Care Unit (NICU) at the University of Minnesota Hospital and Clinic, Minneapolis, in 1982 and 1986 who were subsequently reexamined in the NICU follow-up clinic at age 4 months (corrected for prematurity). The 76 patients represented 47 of the 82 VLBW infants born in 1982 and 29 of the 46 infants born in 1986, representing follow-up rates of 57% and 64%, respectively. These years were chosen for comparison because 1982 represents the year prior to significant changes in cardiorespiratory management in our NICU, and 1986 represents the last year for which 12-month corrected-age follow-up data have been collected and analyzed. All preterm infants hospitalized in our NICU are scheduled at the time of discharge to return to the follow-up clinic at 4 and 12 months corrected age, with the exception of those with multiple congenital anomalies, genetic syndromes, or complex congenital heart disease. The clinical characteristics of the two groups are shown in Table 1.

We obtained neonatal data from the hospital charts as follows: (1) degree of illness at birth in the two study groups using the Physiologic Stability Index (PSI), modified for newborn infants[7,8]; (2) the day parenteral nutrition and enteral feedings were begun, the composition of feedings, feeding-related difficulties, and the mean number of consecutive days from birth that infants in each group received less than 252 kJ/kg/d; and (3) information regarding antenatal treatment with betamethasone sodium phosphate, prevalence of perinatal asphyxia (five-minute Apgar score, <5), prevalence of respiratory distress syndrome, type of mechanical ventilator used, prevalence of patent ductus arteriosus and time of treatment, prevalence of diuretic use, and the duration of physiologic instability as assessed by the number of postnatal days needed to achieve a PSI score of less than 3.

We compared the subsequent nutritional statuses of the two groups of infants at discharge by measuring their weights, lengths, and occipitofrontal circumferences (OFCs) and standardizing them for postconceptional age by z transformation.[9] We also recorded the prevalence of medical conditions in the neonatal period that can affect energy utilization and growth (such as bronchopulmonary dysplasia, necrotizing enterocolitis, severe gastroesophageal reflux requiring Nissen fundoplication, short-bowel syndrome, and severe neurologic impairment characterized by hydrocephalus requiring ventriculoperitoneal shunting or ongoing seizure disorder).

At the 4- and 12-month clinic visits, we recorded (1) the infants' weights, lengths, and OFCs, and, based on their ages corrected for prematurity using the Ross Simulator Calculator (Ross Laboratories, Columbus, Ohio), their calculated mean anthropometric percentiles and their calculated z scores; (2) the prevalence of weights and OFCs below the fifth percentile in each study group; and (3) the infants' current dietary histories, obtained from the parents, and the calculated average daily energy intakes. We performed a modified Amiel-Tison neurologic examination and recorded the number of infants in each group with abnormal neurologic tone.[10] The infants with ab-

Accepted for publication Aug 31, 1988.

From the Division of Neonatology, Department of Pediatrics, University of Minnesota Hospital and Clinic, Minneapolis.

Reprint requests to Box 39, University of Minnesota Hospital and Clinic, Harvard Street at East River Road, Minneapolis, MN 55455 (Dr Georgieff).

normal neurologic examination results were divided into those with findings prognostic of poor developmental outcome (truncal hypotonicity and hypertonicity) and those with findings of less prognostic significance (isolated mild extremity hypertonicity).[11] Infants whose weights or OFCs were below the fifth percentile at 4 months were reassessed at 12 months to determine how many had demonstrated catch-up growth. All infants who returned at age 12 months were assessed using the Bayley Scales of Infant Development.[12]

To assess the changes in the nutritional and neurologic outcomes of preterm infants between 1982 and 1986, we compared the values of the 1982 VLBW infants with those of the 1986 VLBW infants. Comparisons of group means were made by Student's t test, while comparisons of group prevalence were made by χ^2 analysis or Fisher's exact test. All statistical comparisons were considered significant at $P<.05$.

RESULTS

The two groups of VLBW infants were well matched at birth for size, gestational age, degree of illness, need for mechanical ventilation, and prevalence of perinatal asphyxia (Table 1). Their degrees of illness were similar, with no differences in rates of perinatal distress or antenatal betamethasone exposure. Assessment of neonatal clinical factors revealed that, although the two groups of infants were equally ill at the time of admission, the 1982 infants were physiologically more unstable for longer times (Table 2).

The infants were fed similar formulas using similar techniques during the two study periods. Infants were fed dilute soy-based formula for one week, followed by full-strength premature infant formula. Infants weighing less than 1000 g received continuous drip feeding; those weighing more than 1000 g received bolus feeding. Despite these similarities, the 1986 infants were fed earlier at a significantly higher mean PSI score, received parenteral nutrition earlier, and received inadequate energy intakes for a significantly shorter period than the 1982 infants.

Patent ductus arteriosus was treated significantly earlier in 1986 using indomethacin; in 1982, all ducti were surgically ligated. There was no significant difference in the number of infants requiring mechanical ventilation; however, a significantly larger proportion were treated with pressure-preset ventilators (as opposed to volume ventilators) in 1986. Prevalence of diuretic use was similar between years.

Table 1.—Clinical Characteristics of the Study Populations at Birth*

	1982 (n = 47)	1986 (n = 29)
Mean (± SD) birth weight, g	1106 ± 201	1112 ± 242
Mean (± SD) estimated gestational age, wk	28 ± 2	28 ± 3
Birth weight percentile, mean ± SD	50 ± 23	42 ± 28
Birth length percentile, mean ± SD	44 ± 25	41 ± 31
Birth OFC percentile, mean ± SD	50 ± 23	47 ± 26
Admission PSI score, mean ± SD	7.9 ± 3.9	8.0 ± 4.2
% requiring mechanical ventilation	81	79
% exposed antenatally to betamethasone	45	38
% with 5-min Apgar scores of <5	28	14

*There are no significant differences between groups. OFC indicates occipitofrontal circumference; PSI, Physiologic Stability Index.

Table 2.—Clinical Data of Study Infants During Hospitalization*

	1982 (n = 47)	1986 (n = 29)	P
Mean (± SD) duration of PSI score >2, d	13.5 ± 9.5	8.6 ± 7.4	<.01
Mean (± SD) No. of days at <252 KJ/kg/d	14.2 ± 5.7	7.7 ± 3.7	<.001
Day at which parenteral nutrition was started, mean ± SD	4.5 ± 1.7	3.5 ± 1.9	<.01
Day at which enteral nutrition was started, mean ± SD	12.3 ± 9.5	9.3 ± 6.9	<.05
PSI score when enteral nutrition was started, mean ± SD	3.2 ± 2.1	4.0 ± 4.5	<.05
% of ventilated infants with PDA	40	57	NS
Mean (± SD) age at PDA treatment, d	14.5 ± 7.7	6.1 ± 4.5	<.001
Type of mechanical ventilator, pressure/volume	22/16	22/1	<.001
% receiving diuretics	31.9	37.9	NS

*PSI indicates Physiologic Stability Index; PDA, patent ductus arteriosus; and NS, not significant.

At hospital discharge, the 1982 infants were significantly lighter and shorter, with smaller OFCs, than the 1986 infants discharged at the same postconceptional age (Table 3). The prevalence of weights and OFCs below the fifth percentile was significantly higher in the 1982 infants. The 1982 infants had a significantly higher rate of serious medical complications, of which the predominant one was bronchopulmonary dysplasia (n = 12 in 1982; n = 4 in 1986).

At 4 months corrected age, the 1982 infants remained significantly lighter and shorter, with smaller OFCs, than the 1986 infants, despite adequate and similar postdischarge nutritional intakes (Table 4). Significantly more 1982 infants had weights below the fifth percentile at age 4 months. The numbers of infants with abnormally small OFCs were similar between the groups. The percentages of infants with abnormal 4-month neurologic examination results were similar between 1982 (47%) and 1986 (34%). However, of those infants with abnormal examination results, significantly more born in 1982 had truncal tone abnormalities, indicating a worse long-term developmental prognosis (73% vs 30%; $P = .025$).

Thirty-two (68%) of the 1982 infants seen at 4 months returned at 12 months corrected age. Twenty infants who had weights below the fifth percentile at 4 months continued to be abnormally small at 12 months. Eighteen (62%) of the 1986 infants seen at 4 months returned at 12 months. Only five had weights below the fifth percentile, a significantly lower rate than the 1982 infants ($P<.001$) (Table 5). The group of 1982 infants remained significantly shorter and had smaller mean OFCs than the 1986 infants. Weight percentiles were not significantly different between the two groups because of a decrease in percentiles in the 1986 group rather than catch-up growth in the 1982

Table 3.—Growth and Clinical Data at Discharge			
	1982 (n = 47)	1986 (n = 29)	P
Mean (± SD) postconceptional age at discharge, wk	37.3 ± 2.7	36.7 ± 3.6	Not significant
Mean (± SD) discharge weight percentile (z score)	<5 (−2.77 ± 0.43)	10.8 ± 17.2 (−1.96 ± 0.33)	<.001
Mean (± SD) discharge length percentile (z score)	<5 (−2.88 ± 0.14)	7.6 ± 24.5 (−1.99 ± 0.10)	<.001
Mean (± SD) discharge OFC percentile (z score)	8.0 ± 21.2 (−1.99 ± 0.10)	31.9 ± 23.2 (−1.08 ± 0.06)	<.001
No. with weights below 5th percentile at discharge	34	9	<.001
No. with occipitofrontal circumferences below 5th percentile at discharge	21	4	<.01
No. with severe medical complications at discharge	19	5	<.05

Table 4.—Growth and Nutritional Data at Initial Follow-up			
	1982 (n = 47)	1986 (n = 29)	P
Mean (± SD) corrected age at follow-up, mo	3.8 ± 1.3	3.9 ± 0.8	Not significant
Mean (± SD) weight percentile (z score)	10 ± 28 (−1.87 ± 0.41)	33 ± 30 (−1.1 ± 0.24)	<.001
Mean (± SD) length percentile (z score)	10 ± 20 (−1.87 ± 0.15)	28 ± 26 (−1.2 ± 0.10)	<.001
Mean (± SD) occipitofrontal circumference percentile (z score)	32 ± 30 (−1.1 ± 0.24)	58 ± 28 (0.15 ± 0.12)	<.001
No. with weight below 5th percentile	23	7	<.05
No. with occipitofrontal circumference below 5th percentile	6	2	Not significant
Mean (± SD) nutritional intake at 4 mo corrected age, kJ/kg/d	466 ± 88	416 ± 80	<.01

Table 5.—Growth and Development at 12 Months Corrected Age			
	1982 (n = 32)	1986 (n = 18)	P
Mean (± SD) weight percentile (z score)	13 ± 23 (−1.54 ± 0.24)	19 ± 15 (−1.22 ± 0.12)	Not significant
Mean (± SD) length percentile (z score)	18 ± 24 (−1.33 ± 0.06)	30 ± 18 (−1.10 ± 0.04)	<.01
Mean (± SD) occipitofrontal circumference percentile (z score)	25 ± 25 (−1.15 ± 0.19)	43 ± 28 (−0.60 ± 0.21)	<.01
No. of infants with weights below 5th percentile	20	5	<.001
No. of infants with occipitofrontal circumferences below 5th percentile	7	2	Not significant
Mental developmental index score, mean ± SD	81 ± 26	105 ± 22	<.001
Psychomotor developmental index score, mean ± SD	83 ± 21	85 ± 19	Not significant

group. The 1982 infants had lower mental developmental index scores but not lower psychomotor developmental index scores at 12 months.[12] Since there was a substantial decrease in clinic return rates at 12 months, with a possible selection bias toward smaller, more compromised infants, especially in 1986, we chose to compare the developmental outcomes of all infants from the two years who had weights below the fifth percentile at 12 months with the outcomes of the infants whose weight percentiles were normal. The mean mental developmental index and psychomotor developmental index scores,[12] respectively, for the infants with weights below the fifth percentile were 84 ± 27 and 73 ± 21, significantly lower ($P < .005$ for both comparisons) than the scores of the infants with normal weights at 12 months (105 ± 18 and 90 ± 17).

COMMENT

The nutritional status of VLBW infants at hospital discharge and at 4 and 12 months corrected age has improved significantly over a four-year period. In our study population, these improvements were temporally associated with earlier and more aggressive nutritional regimens, significant changes in cardiorespiratory management, and a lower incidence of severe medical complications that could compromise growth. The number of infants in either VLBW group who remained abnormally small at follow-up appeared to be directly related to the number of infants in each group whose weights and OFCs were below the fifth percentile at hospital discharge. Infants who continued to be small at 12 months corrected age had had more neurologic abnormalities detected at 4 months and had poorer developmental status at 12 months. Hack et al[2] have previously shown that poor catch-up growth in VLBW infants is associated with severity of neonatal complications, poor head growth, and chronic physical and neurologic sequelae. The poorer neurologic and developmental outcome of the 1982 infants in our study confirms results of previous studies relating poor neonatal energy intake, chronic physical and neurologic sequelae, and poor first-year somatic and head growth with a greater risk of poor developmental outcome.[2-6]

Infants with birth weights less than 1500 g are particularly likely to suffer inadequate postnatal growth while in a newborn intensive care unit because of high energy requirements, a limited

ability to tolerate enteral nutrition, limited protein-energy reserves, and a high incidence of disorders that increase oxygen consumption, such as bronchopulmonary dysplasia.[13-15] At follow-up, this group of infants has traditionally had the slowest catch-up growth and may require at least three years to achieve weights above the fifth percentile for corrected gestational age.[16,17] Recent advances in perinatal medicine have lowered the rates of bronchopulmonary dysplasia.[18] Concurrently, the development of more vigorous nutritional regimens, including iso-osmolar 101-J/oz formulas and parenteral amino acid solutions designed specifically for newborn infants, have contributed to earlier repletion of nutritional deficits while infants are still in the intensive care nursery.

Adequate postnatal growth occurs when energy delivery significantly exceeds an infant's baseline energy requirements, which in turn are dictated by the infant's degree of illness. Several investigators have determined that 252 kJ/kg/d is a conservative minimum estimate of energy intake necessary to support baseline energy requirements in healthy preterm newborn infants.[19,20] We were able to document several changes in neonatal nutritional and cardiorespiratory management that occurred between 1982 and 1986 that may account for the improvement in nutritional outcome. In 1986, infants received more than 252 kJ/kg/d at an earlier postnatal age, primarily because both parenteral and enteral nutrition were started earlier and enteral feedings were introduced at significantly higher PSI scores. From a respiratory viewpoint, there was a change from volume ventilators to pressure-preset ventilators. Patent ductus arteriosus was diagnosed more frequently and, once diagnosed, was treated at an earlier age. Several studies have demonstrated the high incidence of patent ductus arteriosus in the VLBW infant and the increased incidence of chronic lung disease when treatment is delayed.[21,22]

It is possible that the 1986 group was inherently less ill; however, their PSI scores on day 1 of life suggest that their degrees of physiologic instability (and, therefore, illness) were similar to those of the 1982 group. The relative rapidity with which they improved represents the interaction between their illness at birth and how they were treated postnatally. Since the two groups were equally ill at birth, we speculate that changes in nutritional and respiratory management may have affected the postnatal course of the 1986 infants, significantly shortening the time course of illness, lowering the rates of chronic disease, and allowing these infants to begin adequate postnatal growth at an earlier age.

In summary, our study shows that VLBW infants are being discharged at higher weight, length, and OFC percentiles, and are subsequently being found to have better growth and development at follow-up. We have found coincidental trends toward more aggressive neonatal nutritional management and toward lower incidences of severe chronic medical conditions that could handicap growth.

The authors thank Pi-Nian Chang, PhD, and Becky Schultheis for performing and reviewing the developmental examinations; the nurses of the Pediatric Clinic for measuring the infants at follow-up; Ginny Lyson for editorial assistance; and John Connett for statistical advice.

References

1. Fitzhardinge PM: Follow-up studies of the high-risk newborn, in Avery GB (ed): *Neonatology: Pathophysiology and Management of the Newborn*, ed 3. Philadelphia, JB Lippincott, 1987, pp 400-413.

2. Hack M, Merkatz IR, McGrath SK, et al: Catch-up growth in very-low-birth-weight infants. *AJDC* 1984;138:370-375.

3. Hack M, Merkatz IR, Gordon D, et al: The prognostic significance of postnatal growth in very low-birth weight infants. *Am J Obstet Gynecol* 1982;143:693-699.

4. Ross G, Krauss AN, Auld PA: Growth achievement in low-birth-weight premature infants: Relationship to neurobehavioral outcome at one year. *J Pediatr* 1983;103:105-108.

5. Gross SJ, Oehler JM, Eckerman CO: Head growth and developmental outcome in very low-birth-weight infants. *Pediatrics* 1983;71:70-75.

6. Georgieff MK, Hoffman JAS, Pereira GR, et al: Effect of neonatal caloric deprivation on head growth and one-year developmental status in preterm infants. *J Pediatr* 1985;107:581-587.

7. Pollack MM, Yeh TS, Ruttimann UE, et al: Evaluation of pediatric intensive care. *Crit Care Med* 1984;12:376-383.

8. Georgieff MK, Mills MM, Bhatt P: Validation of two scoring systems which assess the degree of physiologic instability in critically ill newborn infants. *Crit Care Med*, in press.

9. Walpole RE: *Introduction to Statistics*, ed 3. New York, MacMillan Publishing Co Inc, 1982, pp 40-41.

10. Amiel-Tison C, Grenier A: *Neurologic Assessment During the First Year of Life*. New York, Oxford University Press Inc, 1986, pp 180-194.

11. Georgieff MK, Bernbaum JC, Hoffman-Williamson M, et al: Abnormal truncal muscle tone as a useful early marker for developmental delay in low birth weight infants. *Pediatrics* 1986;77:659-663.

12. Bayley N: *Bayley Scales of Infant Development*. New York, The Psychological Corp, 1969.

13. Adamkin DH: Nutrition in very, very low birth weight infants. *Clin Perinatol* 1986;13:419-443.

14. Escobedo MB, Gonzalez A: Bronchopulmonary dysplasia in the tiny infants. *Clin Perinatol* 1986;13:315-326.

15. Weinstein MR, Oh W: Oxygen consumption in infants with bronchopulmonary dysplasia. *J Pediatr* 1981;99:958-961.

16. Hirata T, Epcar JTR, Walsh A, et al: Survival and outcome of infants 501 to 750 gm: A six year experience. *J Pediatr* 1983;102:741-748.

17. Kurzner SI, Garg M, Bautista DB: Growth failure in infants with bronchopulmonary dysplasia: Nutrition and elevated resting metabolic expenditure. *Pediatrics* 1988;81:379-384.

18. Hodgman J: Chronic lung disease, in Avery GB (ed): *Neonatology: Pathophysiology and Management of the Newborn*, ed 3. Philadelphia, JB Lippincott, 1987, pp 446-459.

19. Carlson SE, Barness LA: Protein and energy requirements of term and preterm infants. *J Pediatr Gastroenterol Nutr* 1983;2(suppl):81-86.

20. Georgieff MK, Hoffman J, Pereira GR: Minimal nutritional requirements for ideal head growth and weight gain in premature infants, abstracted. *Pediatr Res* 1983;17:313A.

21. Cotton RB, Stahlman MT, Berder HW, et al: Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. *J Pediatr* 1978;93:647-655.

22. Kappa P, Lanning P, Koivisto M: Early closure of patent ductus arteriosus with indomethacin in preterm infants with idiopathic respiratory distress syndrome. *Acta Paediatr Scand* 1983;72:129-133.

In Other AMA Journals

JAMA

Soda Pop Vending Machine Injuries

M. Q. Cosio (*JAMA* 1988;260:2697)

Reported Sexual Behaviors and Self-esteem Among Young Adolescents

Donald P. Orr, MD; Mary L. Wilbrandt, MSW; Catherine J. Brack, MS; Steven P. Rauch, MSW; Gary M. Ingersoll, PhD

• Six hundred seventy-seven adolescents in grades 7 through 9 of a blue-collar, midwestern junior high school responded to a survey of sexual behavior and self-esteem. The focus of this study was on the relationship between sexual experience and self-esteem. Fifty-five percent of the students reported having had at least one coital experience; 7% reported having intercourse about once a week. The proportion of sexually experienced adolescents increased with age; 28% of 12-year-olds, 52.7% of 13-year-olds, 60.1% of 14-year-olds, 73.6% of 15-year-olds, and 90% of 16-year-olds reported having intercourse on at least one occasion. More boys of all ages were sexually active than girls. Six percent of students had had, or were suspicious of having had, a sexually transmitted disease; 7.8% were involved in a pregnancy. The average of the self-esteem scores for girls was significantly lower than the average for boys. There was an interaction effect between gender and coital history for self-esteem. Girls who reported having had intercourse had lower self-esteem scores than those who did not. On the other hand, self-esteem of sexually experienced and inexperienced boys did not differ, nor did self-esteem of virginal boys and girls. Boys and girls with a history of sexually transmitted diseases had lower self-esteem than all others. Pregnancy, on the other hand, did not seem to affect self-esteem of the sexually experienced adolescents. This cross-sectional study does not permit determination of whether the lower average self-esteem among certain girls was antecedent to or a consequence of sexual experience.

(*AJDC*1989;143:86-90)

The proportion of teenagers who are sexually active remains high. In 1979, 50% of metropolitan, never-married girls 15 to 19 years old and 70% of 17-year-old to 21-year-old men were sexually experienced, that is, reported having ever had intercourse.[1] Furthermore, the proportion of 15-year-old to 19-year-old girls who were sexually experienced increased during the previous decade. Although the data of Zelnik and Kantner[1] offer valuable insights into sexual behavior of typical high school–age youths, generalization to younger populations of socioeconomically diverse adolescents is limited.

Health and socioeconomic problems associated with premature sexual activity are well described. Incidences and prevalence of sexually transmitted diseases (STDs)[2] and premature pregnancy and parenthood[3] are increasing among teens aged 10 to 14 years. However, little is known about psychosocial correlates of sexual activity among young adolescents nor is adequate recent information available about their behaviors. If educational programs encouraging teens to postpone or curtail sexual involvement are to be successful, more must be known. Aiming programs toward younger adolescents based on data drawn from older populations may be inappropriate. Prevention programs delivered to a population at low risk for engaging in a behavior or who see themselves as unlikely to engage in the behavior are likely to be unsuccessful. If relevant psychosocial correlates to at-risk behaviors exist, an intervention no longer needs to be global and nondirected.

The present data are drawn from a survey of midwestern junior high school students. The study was designed to determine the prevalence of self-reported sexual experiences, pregnancy, and STD and their relationships to self-esteem. Previous studies of early dating suggest that precocious dating may be a factor in lowered self-esteem.[4] If early dating is a potential negative influence on self-esteem, it is reasonable to assume that early initiation of coitus could also adversely affect self-esteem. Even among college coeds, first coital experience may lead to lowered self-worth.[5] This study sought to assess differential relationships of sexual experience and self-esteem of early adolescent boys and girls. Because it is a cross-sectional study, direction and causality cannot be determined.

METHODS

Students attending a single junior high school (grades 7 through 9, enrollment 850) in a predominately blue-collar community were surveyed. Sexuality education is taught in grades 1 through 12 in this school system and includes age-appropriate instruction about anatomy and physiology. Questionnaires were administered to all students in all math classes (a mandatory subject) on one day. Students were informed that participation was optional and that all information was anonymous. Written, parental consent was waived with the approval of the Indiana University Committee of the Protection of Human Subjects and the school administration. Informed assent was obtained from each student; parents had been notified by mail that the survey was to be conducted. They and the students could refuse to participate.

Behaviors and experiences covering multiple high-risk activities were self-reported in a format we have used with other junior high school students.[6-9] Students were asked to respond on a four-point ordinal scale (1, nev-

Accepted for publication Aug 29, 1988.

From the Departments of Pediatrics (Dr Orr and Ms Brack) and Counseling and Educational Psychology (Dr Ingersoll), Indiana University Schools of Medicine and Education, Indianapolis, and the Marion County Health Department (Ms Wilbrandt and Mr Rauch), Indianapolis, Ind.

Presented in part at the American School Health Association Annual Meeting, Indianapolis, Ind, Oct 9, 1987.

Reprint requests to Department of Pediatrics, Room A586, James Whitcomb Riley Hospital for Children, 702 Barnhill Dr, Indianapolis, IN 46223 (Dr Orr).

Student-Reported Sexual Behaviors						
	Age, y					
Coitus	**12**	**13**	**14**	**15**	**16**	**Total**
Boys, No. (%)*						
Never	29 (63.0)	28 (28.6)	31 (26.1)	12 (21.4)	0 (0.0)	100 (30.3)
Once	6 (13.0)	22 (22.4)	24 (20.2)	8 (14.3)	0 (0.0)	60 (18.2)
More than once	9 (19.6)	44 (44.9)	53 (44.5)	27 (48.2)	7 (63.6)	140 (42.4)
Frequently	2 (4.3)	4 (4.1)	11 (9.2)	9 (16.1)	4 (36.4)	30 (9.1)
Total	**46** (13.9)	**98** (29.7)	**119** (36.1)	**56** (17.0)	**11** (3.3)	**330** (100)
Girls, No. (%)†						
Never	47 (78.3)	69 (64.5)	62 (54.4)	12 (34.3)	2 (22.2)	192 (59.1)
Once	10 (16.7)	17 (15.9)	22 (19.3)	6 (17.1)	1 (11.1)	56 (17.2)
More than once	2 (3.3)	16 (15.0)	24 (21.1)	12 (34.3)	6 (66.7)	60 (18.5)
Frequently	1 (1.7)	5 (4.7)	6 (5.3)	5 (14.3)	0 (0.0)	17 (5.2)
Total	**60** (18.5)	**107** (32.9)	**114** (35.1)	**35** (10.8)	**9** (2.8)	**325** (100)

*$\chi^2 = 49.632$, $P<.00001$. †$\chi^2 = 45.488$, $P<.00001$.

er, to 4, once a week) to statements such as, "I have had sex/sexual intercourse." Several questions were asked in a yes or no format: "I have been pregnant," "I have gotten someone pregnant," and "I have had or thought I might have had a venereal disease."

For our study, virginal refers to those youth who denied ever having sexual intercourse. Sexually experienced adolescents are those who report at least one coital experience. Sexually active adolescents refers only to those who reported having had sexual intercourse "about once a week." The Rosenberg Self-Esteem Scale[10] was embedded in the questionnaire. This is a ten-item measure of global self-esteem scored on a scale of 1 to 4 points (1, strongly agree, to 4, strongly disagree); total scores ranged from 10 to 40, with higher scores indicating higher self-esteem. The reliability (0.85, test-retest), homogeneity (92% reproducibility, Guttman procedure), and validity of this scale are established; it is recommended as a short, general index of self-esteem.[11] Parental occupation was requested to enable classification of socioeconomic status according to the Hollingshead One Factor Index of Social Position.[12]

Contingency tables with χ^2 statistics were used to examine noninterval level data. The Goodman and Kruskal γ value[13,14] measured the strength of association for ordinal variables. The γ value is similar to a correlation with values from zero to one. Interval level data were analyzed using two-way analysis of variance; the Sheffé criterion was then used as a post hoc test of pairwise differences.[15] The Sheffé is an extremely conservative post hoc test; therefore, $P<.05$ was considered statistically significant.

RESULTS

Six hundred seventy-seven students (80% of the student body) completed the questionnaire. Fifty percent of the sample were male, 77% were white, and 19% were black. Ages ranged from 12 through 16 years with a mean age of 13.6 years (SD = 1.0 year).

As a check for internal validity of responses, the data were examined to assure logical consistency. Twelve adolescents reported being virginal yet answered "yes" to the STD question; nine sexually inexperienced youths reported a pregnancy. One student answered "yes" to questions regarding both conditions, yet denied sexual experience. These 22 students (3.3% of the total sample) were of similar age, gender, race, socioeconomic status, and self-esteem to all other respondents. More reported "questions about sex" (44%) than the other virginal students (36%) although this difference was not statistically significant. It is possible that the 12 reportedly virginal students were concerned about STD acquired through noncoital activities. While the inclusion of these 22 cases did not alter the results with respect to self-esteem, only the data from the remaining 655 students are reported here.

Fifty percent of the students reported living with both parents, 24% lived with a parent and a stepparent, 13% lived with the father only, and 23% with the mother only. Of those providing information about maternal occupation (n = 483), 46% reported mothers having unskilled jobs, 21% had semiskilled jobs, 23% had skilled work, and 10% had minor-professional or professional employment. Fathers (n = 433) were reported by 22% to be unskilled workers, by 37% to be semiskilled, by 32% to be skilled laborers, and by 9.0% to be minor-professionals or professionals.

There were several differences on sociodemographic variables between black and white students. More black students (42%) reported fathers holding unskilled jobs than whites (17%) ($\chi^2 = 23.80$; $P<.001$) and fewer had professional jobs. There was no difference between blacks and whites in the classification of maternal employment. Black students (48%) were more likely to live with a single parent than white students (17%) ($\chi^2 = 63.57$; $P<.0001$). Significantly more black (30%) than white (13%) students reported using Medicaid for health care ($\chi^2 = 20.01$; $P<.0001$), a reflection of living with a single mother. Eighty-six percent of all students had visited a physician within the past 12 months; only 4% had visited for contraception.

Sexual Behaviors

Overall, 293 (45%) of the students reported never having had coitus. Eighteen percent reported having had intercourse once, 30% more than once, and 7% about once a week. Significantly more boys (70%) than girls (41%) claimed sexual experience with 42% of the boys reporting more than one coital experience and 9% reporting regular sexual activity compared with 18% and 5% of the girls, respectively. The proportion of sexually experienced and sexually active youths increased with age

as shown in the Table. With increasing age, a significantly greater proportion of sexually experienced boys and girls were also sexually active.

Although there were no significant differences between white and black girls in the proportion reporting sexual experiences, significantly more black males (80%) than white males (63%) were sexually experienced ($\chi^2 = 8.545$; $P < .01$). The number of black males (n = 77), however, was too small to determine with statistical accuracy whether there were racial differences in the degree of sexual experience. No significant relationships were found between reported sexual experiences and socioeconomic status as indicated by parental occupation, reported living arrangements, or the use of Medicaid.

STD and Pregnancy

Eight percent of the students (n = 55) reported having had or suspected having had STD. There were no differences by race, gender, or age. Adolescents who were more sexually active were more likely to have reported an STD ($\gamma = 0.66$). Sixty-three students (9%) (6% of girls, 12% of boys) had been pregnant or had impregnated someone. There were no differences between black and white students in reported pregnancies. The likelihood of pregnancy increased with frequency of coitus ($\gamma = 0.86$).

Questions About Sex

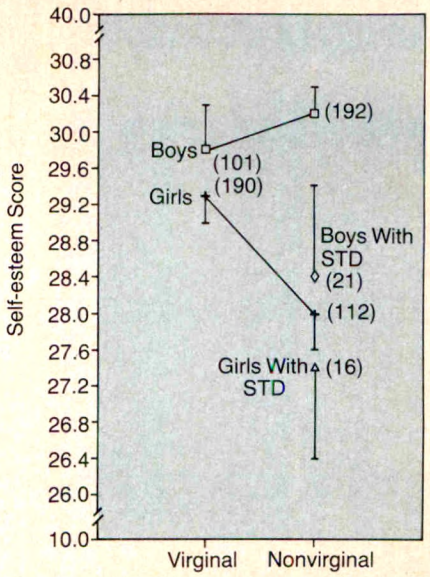
Thirty-one percent of the students responded that they had "questions about sex." There was no difference by age. More black students (42%) ($\chi^2 = 8.49$; $P = .0036$) and girls (38%) ($\chi^2 = 14.06$; $P = .0002$) answered "yes" to this question. Fewer sexually experienced adolescents (26%) than virgins (36%) had questions ($\chi^2 = 97.83$; $P = .0058$). Fifty-one percent of those who believed they had had an STD had questions as compared with 29% of those who did not ($\chi^2 = 16.97$; $P = .0014$). There was no difference between those reporting a pregnancy and those not.

Self-esteem

Self-esteem scores ranging from 10 to 40 were available for 632 adolescents with a mean of 29.36 (SD = 4.40). These 23 students without self-esteem scores were similar to the others with respect to age, gender, race, and sexual behavior. Initially, analysis of sex by four levels of sexual experience was attempted but serious cell size disproportionality among the three sexually experienced groups for boys and girls confounded the results. Hence, the analysis was simplified to a 2×2 analysis of variance where gender and coital experience (yes, no) were analyzed. It was expected that coital experience would have different meanings for male and female early adolescents. Further, self-esteem was analyzed within the sexually experienced group to assess the relationships of having had a venereal disease and having been or having caused a pregnancy. F values are those from analysis of variance.

The impact of a pregnancy on self-esteem of the sexually experienced adolescents appears to have been negligible ($F < 1.0$), neither did the experience differentially affect boys and girls ($F < 1.0$). Venereal disease experience, however, apparently had a negative impact on self-esteem for both boys and girls ($F = 5.22$; $P < .05$). Because venereal disease experience is a contaminant of sexual experience, those students reporting venereal disease experience were excluded from the gender by coital experience analysis.

The analysis of variance of gender by coital experience revealed no overall statistical difference in self-esteem of sexually experienced and virginal adolescents ($F = 1.16$) and significantly higher self-esteem for boys ($F = 15.83$; $P < .001$). The significant gender by coital experience interaction ($F = 5.24$, $P = .03$), however, indicated differential impact of coital experience on self-esteem. Subsequent pairwise comparisons using a Sheffé criterion (criteria)[15] of self-esteem scores for virginal and sexually experienced boys and girls revealed that self-esteem of sexually experienced boys (mean = 30.28; SEM, 0.27) and virginal boys (mean = 29.81; SEM, 0.54) did not differ significantly ($s < 1.0$) while self-esteem of sexually active girls (mean = 28.04; SEM, 0.36) was significantly lower than that of virginal girls (mean = 29.28; SEM, 0.30) ($s = 2.37$, $P < .025$). Viewed from the perspective of virginal and sexually experienced groups, no differences in self-esteem were seen between virginal boys and girls ($s = 1.08$) while significantly lowered self-esteem was seen in sexually experienced girls when compared with sexually experienced boys ($s = 4.46$, $P < .001$). The nature of gender by coital experience initiation is displayed in the Figure. Inclusion of the smaller subgroups of students who reported venereal disease experience did not alter the results. Their numbers were sufficiently small compared with the group that did not, that even were there an effect, the small size was insufficient to reveal it in this context. Furthermore, when male and female students who had an STD are superimposed in the Figure, it may be seen that both genders showed suppressed self-esteem.



Self-esteem and coital status. Values indicate group means; bars, SEM; and numbers in parentheses, number of subjects in each group.

COMMENT

Our survey revealed that sexual activity was commonly reported among these young adolescents. Over 50% of students in grades 7 through 9 were sexually experienced; 18% reported intercourse only once, 30% more than once, and 7% frequently. More boys than girls were sexually active at all ages. Sexually inexperienced boys were in the minority by age 13 years and sexually inexperienced girls were in the minority by age 15 years. This was true

regardless of socioeconomic status, irrespective of whether socioeconomic status was reflected by parental occupation, family living arrangements, or use of Medicaid for health care. The only association with race was that more black males reported having been sexually experienced. Previous researchers have usually been unable to separate the effects of race and socioeconomic status on adolescent sexual behavior.[5,16] In the same fashion, we were limited to the extent that the number of black students in the school was small (19%), and blacks were slightly more disadvantaged than whites, making multivariate statistical comparisons difficult. However, we found minimal differences in reported sexual behaviors or their consequences between black and white students.

Comparison with other data is difficult because little information about sexual behaviors is available for young, nonimpoverished adolescents. In 1973, Vener and Stewart[17] found that 33% of 13- to 15-year-old boys and 17% of girls in two midwestern communities had engaged in coitus. Sorensen,[18] in a study based on a national probability sample, found rates of 44% and 30%, respectively. It has been suggested that the Sorensen sample was not representative of sexual experiences because of a 53% loss of respondents, thus falsely elevating the rates.[17] Zelnik and Kantner[1] found that 22% of 15-year-old, never-married, urban adolescent girls were sexually experienced in 1979 compared with 14% in 1971. They did not present data on boys under 17 years old. More recently, Irwin and Millstein[19] indicated that 32% of students attending a San Francisco junior high school of diverse self-esteem scores and racial composition were sexually active. This rate is much lower than those of 84% for boys and 49% for girls attending an inner-city, all-black Baltimore junior high school.[16] Race and socioeconomic status potentially were confounded in that study because almost all of the students were impoverished. Nevertheless, these reports and our data suggest that more adolescents may be sexually experienced at younger ages than a decade ago.

In their analysis of sexually experienced and virginal youths, Jessor and Jessor[20] reported higher self-esteem among sexually experienced boys but no differences were noted for girls. Jessor and Jessor suggested that among boys higher self-esteem in concert with other problem behaviors, including drug and alcohol use and antisocial acts, predisposed boys to earlier sexual activity. The same link was not found for girls. The Jessors' data, however, were based on an older sample than that used in the present study. In a prevalence study of psychiatric disorder among 150 14- to 16-year-old adolescents, Kashami et al[21] found that adolescents with psychiatric disorders were more likely to be sexually active and to have lower self-esteem. They did not examine relationships between self-esteem and sexual experience, nor whether there were gender differences present. Irwin and Millstein[19] add that some at-risk behaviors have positive benefits for young adolescents.

Our data do not conform to the Jessors'[20] or to the Irwin and Millstein[19] suggestion. The moderately higher self-esteem among sexually active boys when compared with virginal boys was not statistically significant. Since the sample is sufficiently large, it is unlikely that failure to demonstrate a difference was a function of statistical power. A comparison of self-esteem of sexually experienced boys and girls did show major differences. The differences, however, are a function of lowered self-esteem among sexually experienced young adolescent girls. The impact of STD on self-esteem of sexually experienced adolescents was uniformly negative.

We believe these findings may be reflective of basic differences in the meanings of sexual behavior between the sexes. Several investigators have demonstrated gender differences in the response to puberty and other social transitions. It appears that girls enter puberty (as indicated by the physical sexual changes) with lower self-esteem than boys[22,23] and consistently report more negative responses to these events.[23,24] Simmons and Blyth[25,26] demonstrated that pubertal events are but one of multiple "simultaneous" transitions that act in concert to affect self-esteem. Sexual behaviors are rarely included as factors potentially important to self-esteem. Our data suggest that sexual experiences may be important.

Our study was cross-sectional and thus we cannot determine whether suppressed self-esteem among the girls was antecedent to or a consequence of sexual experience or whether it is mediated by a third factor, such as psychiatric disorder. Nevertheless, this would still not explain the gender difference we observed. Some data suggest that changes in self-esteem may follow the transition to sexual activity for young adolescents; boys generally view their first sexual experience more positively than do girls.[18] There are also gender differences in the meaning of puberty,[25-28] which may affect young adolescents' interpretation of the significance of the sexual experiences. Our finding that both boys and girls reporting a history of STD had lower self-esteem than other sexually experienced youth suggests that lower self-esteem follows acquisition (or suspicion) of the infection. It seems unlikely that low self-esteem predisposes to infection since boys who reported regular intercourse had the highest self-esteem and were at greatest risk for infection. We have previously reported[29] that there was a small but significant correlation of problem behaviors with self-esteem such that boys with the highest self-esteem were least likely to engage in these groups of behaviors (and yet more likely to be sexually active). We found no correlation between self-esteem and problem behaviors for girls. If early sexual activity precedes changes in self-esteem, then these findings are consistent with the perpetuation of the double standard that rewards permissiveness for boys but not for girls. Future longitudinal studies will answer this question.

There are several limitations to our study in the degree to which the results may be generalizable. The population we sampled appeared representative of the student body in this blue-collar community junior high school. The majority of students participated, but it is possible that nonresponders could have systematically biased the results in one direction or the other. Although parents and students knew that a survey was to be conducted and had access to the questionnaire, they only knew that it was about health and health behaviors, and contained sensitive ques-

tions. The accuracy of self-report is always an issue. We are not aware of similar data for comparison, but it has been shown that adolescents respond honestly to other sensitive questions, such as substance use.[30,31] Our students' responses to other questions such as use of illicit substances, suicide, family problems, and sexual abuse were identical to those obtained in two other studies of socioeconomically similar schools in the county.[6-8] Our previous experience with this age group suggests that students understand the questions about sexual behavior. They were straightforward, and family life education is included in this school system for grades 1 through 12. Very few students (ten of 677 reported a virginal pregnancy) answered in a fashion that indicated misunderstanding or intentional misrepresentation. There is no way to determine the proportion of students who intentionally overreported or underreported—a problem inherent to sensitive survey research. It is possible that pubertal timing effects may have confounded the findings because it has been suggested that early puberty is related to earlier engagement in sexual activity.[19,25,32] We were not able to assess pubertal status in this study.

Premature sexual activity will remain a problem for American youth. Although solutions will be complex, increased understanding of normal adolescent development may provide the framework for the development and evaluation of future interventions. Our data suggest that education designed to postpone sexual behaviors may need to target an age group younger than junior high school and that gender differences, probably related to the meaning of sexuality, may be important. The small, but statistically significant, differences in self-esteem suggest areas for further longitudinal research.

We thank the school administration, students, and parents who supported and participated in the study, and Paula Kirchner for her secretarial assistance.

References

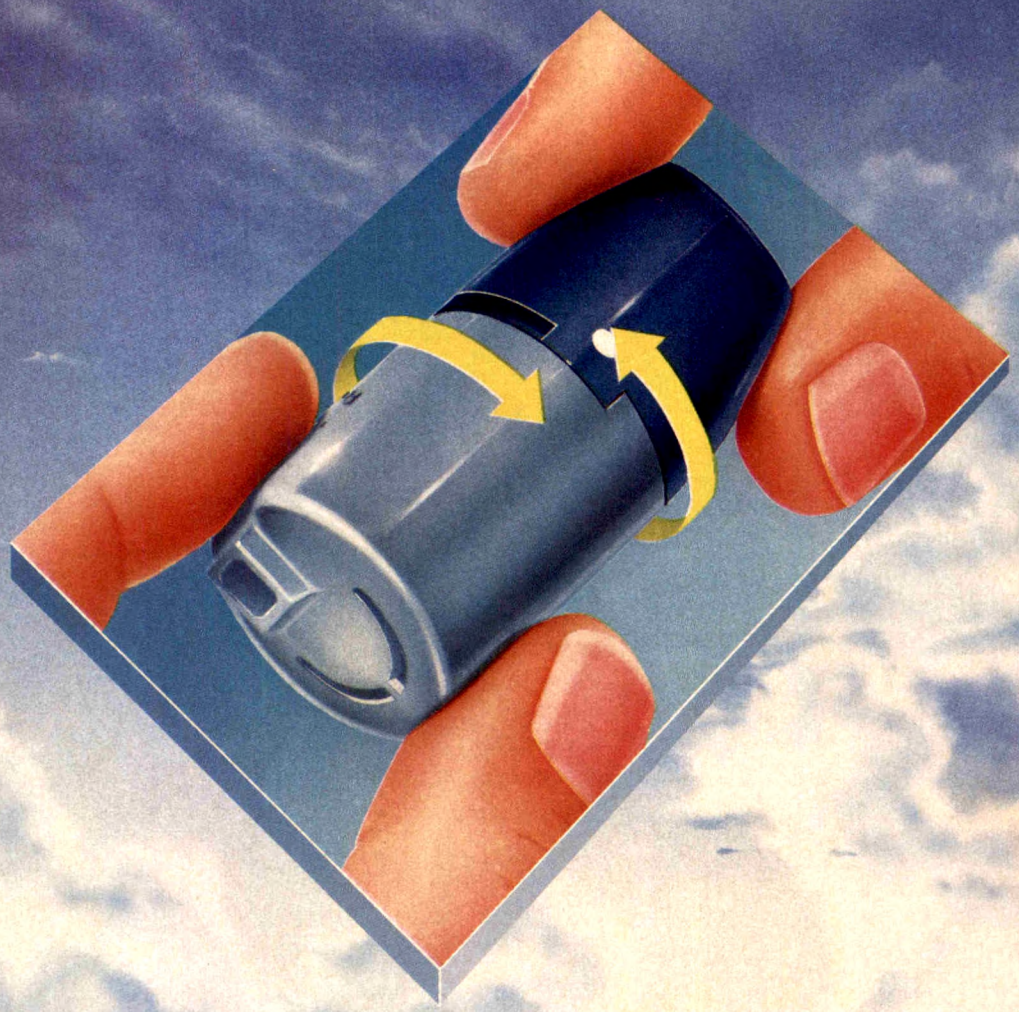
1. Zelnik M, Kantner JF: Sexual activity, contraceptive use and pregnancy among metropolitan-area teenagers: 1971-1979. *Fam Plann Perspect* 1980;12:233-237.
2. Bell T, Hein K: Adolescents and sexually transmitted diseases, in Holmes K, Mardh PA, Sparling P, et al (eds): *Sexually Transmitted Disease*. New York, McGraw-Hill International Book Co, 1984, p 73-84.
3. Jones EF, Forrest JD, Goldman N, et al: Teenage pregnancy in developed countries: Determinants and policy implications. *Fam Plann Perspect* 1985;17:53-63.
4. Simmons RG, Blyth DA, Van Cleave EF, et al: Entry into early adolescence: The impact of school structure, puberty, and early dating on self-esteem. *Am Sociol Rev* 1979;44:948-967.
5. Bell TR, Chasten JB: Premarital sexual experience among coeds, 1958 and 1968. *J Marr Fam* 1970;32:81-84.
6. Weiser SP: *Adolescents' Use of Health Services*, dissertation. West Lafayette, Ind, Purdue University, 1985.
7. Orr D, Lay P, Green M: High risk behaviors among young adolescents: Results from a community survey. Presented to the Program to Consolidate Health Services for High Risk Young People, Warrenton, Va, July 23, 1984.
8. Brack C, Orr D, Ingersoll G: Pubertal maturation and adolescent self-esteem. *J Adolesc Health Care* 1988;9:280-285.
9. Hibbard R, Brack C, Rauch S, et al: Abuse, feelings, and health behaviors in a student population. *AJDC* 1988;142:326-330.
10. Rosenberg M: *Society and the Adolescent Self-Image*. Princeton, NJ, Princeton University Press, 1965.
11. Robinson JP, Shave PR (eds): *Measures of Social Psychological Attitudes*. Ann Arbor, Mich, Institute for Social Research, 1974, pp 98-99.
12. Hollingshead A, Redlich F: *Social Class and Mental Illness: A Community Survey*. New York, John Wiley & Sons Inc, 1958.
13. Johnson AG: *Social Statistics Without Tears*. New York, McGraw-Hill International Book Co, 1979, pp 97-99.
14. Nie NH, Hull CH, Jenkins JG, et al: *Statistical Package for the Social Sciences*, ed 2. New York, McGraw-Hill International Book Co, 1975, pp 228-229.
15. Kirk RE: *Experimental Design: Procedures for the Behavioral Sciences*. Belmont, Calif, Brooks/Cole, 1968.
16. Zabin L, Hirsch M, Smith E, et al: Adolescent pregnancy-prevention: A model for research and evaluation. *J Adolesc Health Care* 1986;7:77-87.
17. Vener AM, Stewart CS: Adolescent sexual behavior in middle America revisited: 1970-1973. *J Marr Fam*, November 1974, pp 728-735.
18. Sorensen RC: *Adolescent Sexuality in Contemporary America*. New York, World Publishing, 1973, pp 189-215.
19. Irwin CE, Millstein SG: Biopsychosocial correlates of risk-taking behaviors during adolescence. *J Adolesc Health Care* 1986;7(suppl):82S-96S.
20. Jessor SL, Jessor R: Transition from virginity to non-virginity among youth: A social-psychological study over time. *Develop Psychol* 1975;11:473-484.
21. Kashami JH, Beck NC, Hoeper EW, et al: Psychiatric disorders in a community sample of adolescents. *Am J Psychiatry* 1987;144:584-589.
22. O'Malley PM, Backman J: Self-esteem: Change and stability between ages 13 and 23. *Develop Psychol* 1983;19:257-268.
23. Tobin-Richards M, Boxer A, Peterson A: The psychological significance of pubertal changes and sex differences in perceptions of self during early adolescence, in Brooks-Gunn J, Petersen A (eds): *Girls at Puberty*. New York, Plenum Publishing Corp, 1983, pp 127-154.
24. Blyth D, Simmons R, Zakin D: Satisfaction with body image for early adolescent females: The impact of pubertal timing within different school environments. *J Youth Adolesc* 1985;14:207-225.
25. Simmons RG: Social transition and adolescent development. *New Dir Child Dev* 1987;37:33-62.
26. Simmons RG, Blyth DA: *Moving Into Adolescence: The Impact of Pubertal Change and School Context*. Hawthorne, NY, Aldine Publishing Co, 1987.
27. Brooks-Gunn J, Warren MP: Measuring physical status and timing in early adolescence: A developmental perspective. *J Youth Adolesc* 1985;14:163-189.
28. Brooks-Gunn J, Warren MP: Biological contribution of affective expression in young adolescent girls. Read before the Biennial Meeting of the Society for Research in Child Development, Baltimore, April 24, 1987.
29. Orr D, Ingersoll G: Adolescent development: A biopsychosocial perspective. *Curr Probl Pediatr* 1988;8:443-487.
30. Campanelli PC, Dielman TE, Shope JT: Validity of adolescents' self-reports of alcohol use and misuse using a bogus pipeline procedure. *Adolescence* 1987;22:7-22.
31. Silber TJ, Getson P, Ridley S, et al: Adolescent marijuana use: Concordance between questionnaire and immunoassay for cannabinoid metabolites. *J Pediatr* 1987;111:299-302.
32. Magnusson D, Staltin H, Allen VL: Biological maturation and social development: A longitudinal study of some adjustment processes from midadolescence to adulthood. *J Youth Adolesc* 1985;14:267-284.

Quotables:

Reading and Lectures: *Physicians, who were formerly encouraged to read medical journals, are now encouraged to attend lectures, despite the fact that they can read five times faster than the lecturer can speak.*

JOSEPH D. SAPIRA
Perspectives in Biology and Medicine 1982

COMING SOON...



NEW **VENTOLIN ROTACAPS®** FOR INHALATION
(ALBUTEROL SULFATE)
AND
ROTAHALER® INHALATION DEVICE

Exclusively from
Allen & Hanburys™
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

Printed in USA
VIN 362

September 1988

NEW

CHILDREN'S NyQuil®

More of what puts cough and congestion to rest

For the cough and congestion that always seem to be at their worst at bedtime, now there's new CHILDREN'S NYQUIL. It's so effective at relieving symptoms that it lets children rest comfortably through the night.

CHILDREN'S NYQUIL has the maximum allowable dosage of three effective medicines: 15 mg dextromethorphan for cough control, 30 mg pseudoephedrine for decongestion, and 2 mg chlorpheniramine for rhinorrhea.

All in a great-tasting, cherry-flavored liquid that children themselves prefer 7 to 1 over the leading cough suppressant/expectorant.

For children ages 6-11, the recommended dosage is one tablespoon every 6-8 hours; ages 2-5, ½ tablespoon; under age 2, dose at your discretion.

CHILDREN'S NYQUIL.
Just what children need when they need it most.

NEW

ALCOHOL-FREE ASPIRIN-FREE

6-8 hours of symptomatic relief from each easy-to-measure dose

maximum children's dosage for restful relief

© 1988 Richardson-Vicks, Inc.
A Procter & Gamble Company

For further information about CHILDREN'S NYQUIL, call toll-free: 1-800-358-8707 (in Ohio, call 1-800-346-9101).

Radiological Cases of the Month

Charles A. Bullaboy, MD; Rufus B. Jennings, Jr, MD;
David H. Johnson, MD; John D. Coulson, MD (*Contributors*);
Lionel W. Young, MD (*Editor for This Case*);
Beverly P. Wood, MD (*Section Editor*)

A 13-year-old boy was admitted to the hospital with a two-day history of polyuria, vomiting, and weakness. His paternal grandparents had diabetes of adult onset. Although two weeks previously he had weighed 43.6 kg at a prefootball physical examination, his weight at admission was 38.2 kg. He was tachypneic (36 breaths per minute) and hyperpneic. His skin and mucous membranes were dry, and soft tissue in his left axilla was crepitant. A systolic crunch was auscultated at the cardiac apex. The initial blood glucose level was 71.3 mmol/L, while the level of glucose in the urine was greater than 55.5 mmol/L, and the urine ketone level was greater than 13.7 mmol/L. Arterial blood pH was 7.19, with a carbon dioxide pressure of 23 mm Hg and an oxygen pressure of 126 mm Hg. Chest roentgenograms (Figure) were obtained.

Accepted and edited for publication by Lionel W. Young, former section editor, May 18, 1987.

Contributed from the Department of Pediatric Cardiology, Children's Hospital of the King's Daughters, Norfolk, Va.

Reprint requests to Department of Radiology, Children's Hospital Medical Center of Akron, 281 Locust St, Akron, OH 44308 (Dr L. W. Young).

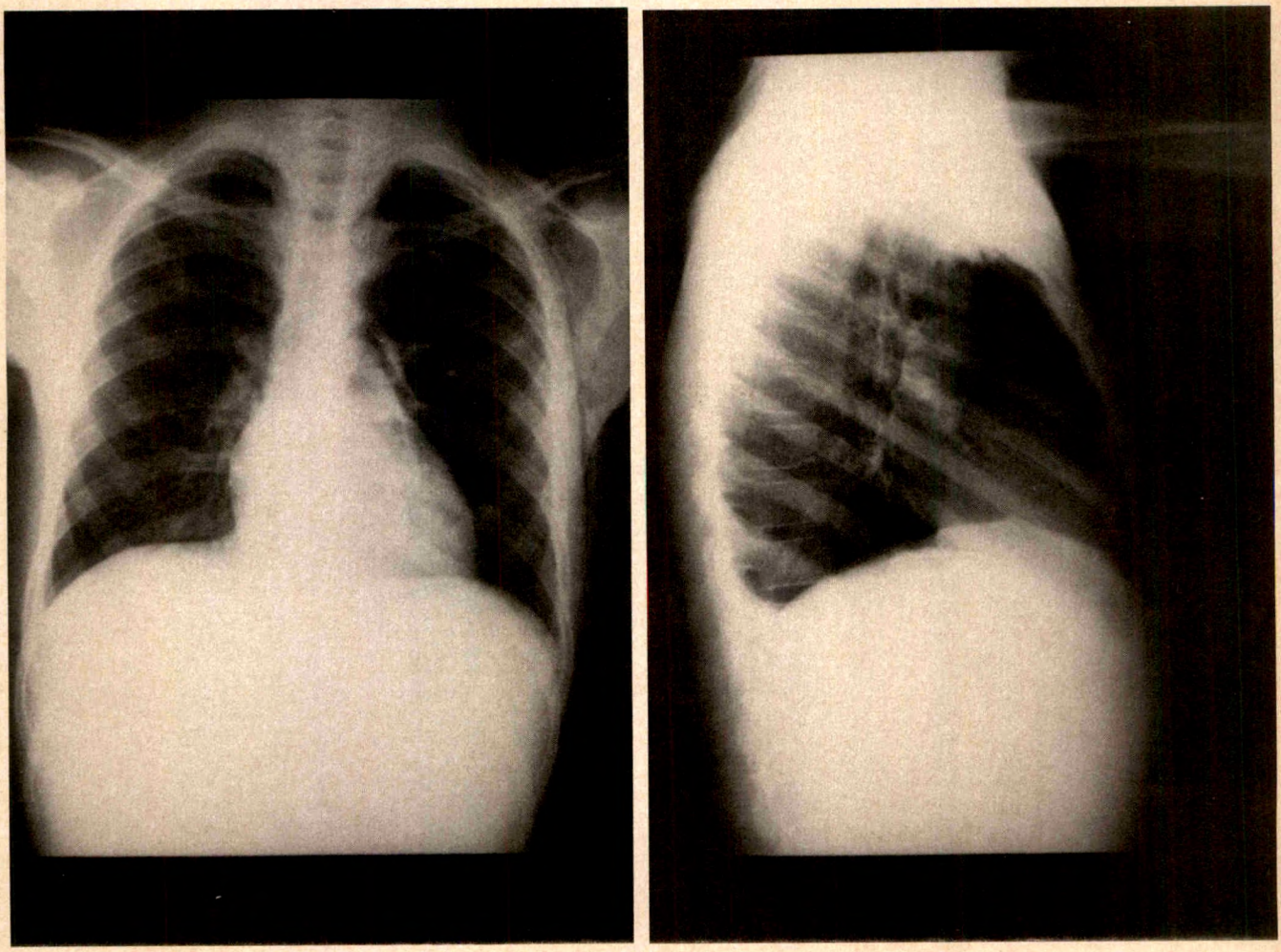


Figure.

Denouement and Discussion

Pneumomediastinum and Subcutaneous Emphysema Caused by Diabetic Hyperpnea

Posteroanterior chest (left) and lateral chest (right) roentgenograms show air in mediastinum and subcutaneous emphysema of left chest wall.

Overproduction of beta-hydroxybutyric and acetoacetic ketoacids in diabetes mellitus leads to metabolic acidosis. To compensate for this disturbance in the acid-base balance, excessive CO_2 is eliminated by rapid and deep Kussmaul's respiration.

Deep breathing produces high intra-alveolar pressures in the range of 20 to 30 mm Hg. Excessive pressure ruptures alveoli and causes air to dissect the perivascular sheaths and spread to the hila of the lungs and the mediastinum.[1] From the mediastinum, air may enter the endothoracic and cervical fascial planes and subcutaneous tissues.[2]

Pneumomediastinum, a rare complication of diabetic ketoacidosis,[3] is usually associated with acute or chronic pulmonary disease. Nonrespiratory causes of pneumomediastinum include penetrating chest trauma, esophageal perforation, hyperemesis, pneumoencephalography, dental extraction, and obstetric delivery.[4] Successful treatment is best achieved by controlling the underlying process that triggers the air leak. Resorption of such leaked air is usually complete within five to seven days. It resorbed in six days in this patient.

References

1. Macklin CC: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum: Clinical implications. *Arch Intern Med* 1939;64:913-926.
2. Bierman CW: Pneumomediastinum and pneumothorax complicating asthma in children. *AJDC* 1967;114:42-50.
3. McNicholl B, Murray JP, Egan B, et al: Pneumomediastinum and diabetic hyperpnoea. *Br Med J* 1968;4:493-494.
4. Munsell WP: Pneumomediastinum: A report of 28 cases and review of the literature. *JAMA* 1967;202:689-693.

Arun K. Pramanik, MD, Sarita Sharma, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A newborn male infant weighing 900 g was admitted to the intensive care unit at 8 hours of age with a diagnosis of prematurity and severe respiratory distress. He was delivered by cesarean section at 28 weeks' gestation to a 23-year-old mother. The Apgar scores were 2 and 3 at one and five minutes, respectively. The infant was intubated with difficulty following several unsuccessful attempts using an endotracheal tube that had an internal diameter of 2.5 mm and a metal stylet. At admission, the patient was in acute respiratory distress and required high ventilator pressures and oxygen.

Repeated efforts to pass a 5-F orogastric tube met with resistance after 6 cm was introduced. After a nasogastric tube was placed in the stomach a chest roentgenogram was obtained (Fig 1). A roentgenogram of the chest was repeated (Fig 2) after instillation of 1 mL of water-soluble contrast material in the nasogastric tube.

Accepted for publication Feb 3, 1988.
Contributed from the Department of Neonatology, Louisiana State University Medical School, Shreveport.
Reprint requests to Department of Radiology, Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

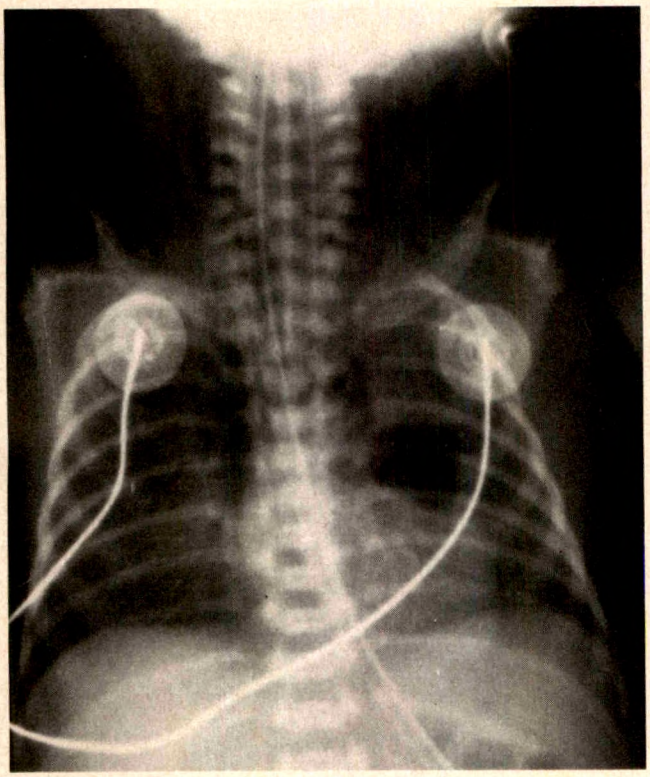


Figure 1.

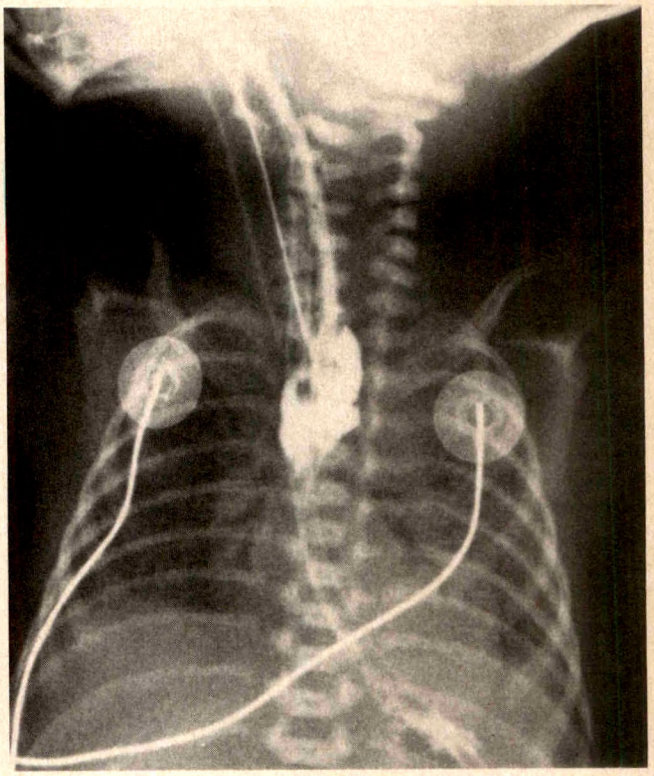


Figure 2.

Denouement and Discussion

Traumatic Hypopharyngeal Pseudodiverticulum

Fig 1.—Chest roentgenogram shows endotracheal tube with its tip at level of T3 vertebra and nasogastric tube with tip in stomach. Pneumomediastinum and subcutaneous air dissection into neck are present. Lungs are slightly underexpanded and show mild changes of respiratory distress syndrome.

Fig 2.—After instillation of contrast material, chest roentgenogram shows it collected in traumatic pseudodiverticulum of hypopharynx.

Traumatic perforation of the hypopharynx was described by Eklöf et al[1] in 1969. It often results from resuscitative efforts involving traumatic endotracheal or gastric intubation with perforation of the laryngoesophageal membrane.[2,3] It has been described following oropharyngeal suctioning at birth or trauma from introduction of the obstetrician's finger during breech deliveries.[2,3] Insertion of any foreign body into the hypopharynx produces reflex constriction of the cricopharyngeus muscle and subsequent attempts to pass a catheter or tube may lead to perforation of the oropharynx proximal to this sphincter.[2,3] Other factors contributing to perforation of the hypopharynx include the rigidity of an endotracheal tube, the use of metal stylets, lack of skill of the individual performing intubation, strong external laryngeal pressure or hyperextension of the infant's neck during intubation, and laryngotracheal anomalies.[4,5]

Early clinical signs of perforation of the hypopharynx and development of a pseudodiverticulum include aspiration of blood-tinged secretions or accumulation of fresh blood in the oropharynx. The clinical findings of traumatic pseudodiverticulum may mimic those of esophageal atresia, including excessive salivation, choking, feeding difficulty, and tachypnea.[2] In those infants with pneumomediastinum or subcutaneous emphysema who have clinical findings suggestive of esophageal atresia, the diagnosis of pharyngeal perforation should be considered.[3,5,6]

The unusual configuration of mediastinal air density seen in Fig 1 and persisting on repeated chest roentgenograms suggests hypopharyngeal air loculation from perforation. Contrast studies or endoscopy may be necessary to confirm the diagnosis and to localize the level of perforation. Cautious laryngoscopy will allow visualization of the traumatic perforation at the level of the cricopharyngeus muscle.[2] The differential diagnosis includes esophageal atresia, congenital true or pulsion diverticulum of the posterior pharynx, and duplication of the esophagus. Contrast radiography may be necessary to differentiate these entities.

The patient management is conservative, consisting of broad-spectrum antibiotic treatment, intravenous fluids, and supportive respiratory therapy. Direct treatment of a pneumopericardium or pneumomediastinum is usually not indicated. Traumatic perforation of the hypopharynx is treatable, and if recognized early should have an excellent prognosis. This condition is preventable if adequately trained persons are providing emergency care at delivery and if resuscitation and use of stylets during intubation are avoided.[3]

References

1. Eklöf O, Löhr G, Okmian L: Submucosal perforation of the esophagus in the neonate. *Acta Radiol Diagn* 1969;8:187-192.
2. Talbert JL, Rodgers BM, Felman AH, et al: Traumatic perforation of the hypopharynx in infants. *J Thorac Cardiovasc Surg* 1977;74:152-156.
3. Touloukian RJ, Beardsley GP, Ablow RC, et al: Traumatic perforation of the pharynx in the newborn. *Pediatrics* 1977;59:1019-1022.
4. Amodio JB, Berdon WE, Abramson SJ, et al: Retrocardiac pneumomediastinum in association with tracheal and esophageal perforations. *Pediatr Radiol* 1986;16:380-383.
5. McLeod BJ, Sumner E: Neonatal tracheal perforation: A complication of tracheal intubation. *Anaesthesia* 1986;41:67-70.
6. Wells SD, Leonidas JC, Conkle D, et al: Traumatic prevertebral pharyngoesophageal pseudodiverticulum in the newborn infant. *J Pediatr Surg* 1974;9:217-222.

The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

THE COUGH STOPS HERE.

Stops coughs cold.

Triaminic-DM® stops coughs cold with centrally acting dextromethorphan. It's as effective as codeine, without codeine's side effects.[1-3†]

A proven decongestant clears stuffy noses and reduces phlegm that runs down the throat, causing irritation.

Without alcohol.

Triaminic-DM is 100% alcohol free. No unnecessary ingredients. No drowsiness.

PEDIATRICIAN #1 RECOMMENDED

Triaminic-DM®
COUGH FORMULA

Stops coughs. Without alcohol.

†Except in severe cough

References:

1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986, pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharmacy Times* 1985;51(1):80-90.

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

Safety of Newborn Discharge in Less Than 36 Hours in an Indigent Population

Paul D. Conrad, MD; Randall B. Wilkening, MD; Adam A. Rosenberg, MD

• The safety of a moderately early newborn discharge program and the ability to follow up within 48 hours of release was evaluated in an indigent population from our institution. A retrospective chart review of 2000 consecutive admissions to our normal newborn nursery was conducted to determine the following: (1) length of nursery stay; (2) reason for extension of nursery stay beyond 36 hours; (3) documentation of outpatient follow-up within 48 hours of discharge for infants released within 36 hours of birth; and (4) incidence of and reason for readmission to the hospital within one week of initial discharge. A total of 1091 infants (54.6%) were discharged within 24 to 36 hours of birth, with documentation of outpatient follow-up in 994 (91.1%). Twenty-five (2.3%) of the early discharges required readmission within seven days of initial discharge compared with a 0.89% incidence among infants hospitalized greater than 48 hours. Twenty-four of the 25 readmissions did have outpatient follow-up, and no serious complications occurred. The data demonstrate that moderately early neonatal discharge can be safely accomplished in an indigent population with the aid of a successful outpatient follow-up program.

(*AJDC* 1989;143:98-101)

The recognition of wellness associated with a normal birthing process of the full-term infant has led to a shortening of the postpartum stay for both mother and child.[1,2] A hospital-based delivery is advisable to assure the safety of all infants.[3] However, once an uncomplicated birth is completed and a stable transition has occurred, there appears to be little further benefit of prolonged hospitalization for the healthy term infant born to parents in the middle and upper socioeconomic classes.[4,5]

The purpose of this study was to determine whether an abbreviated (24 to 36 hours) neonatal postpartum hospitalization was adequate to assure the relative safety of the normally born infant from a university hospital–based clinic population. We sought as well to determine the ability to provide an outpatient contact within 48 hours from the time of discharge.

METHODS

In conjunction with the implementation of outpatient nursing services provided to both the mother and newborn infant by a single individual, maternal and infant criteria were delineated for early discharge from our institution (Table 1). Maternal education in the immediate postpartum period included instruction on feeding (breast or bottle), formula preparation, cord and circumcision care, care of common infant problems (eg, diaper rash), car seat instruction, signs of illness and common newborn problems (eg, jaundice), normal infant sleep patterns, and the importance of follow-up care. Maternal competence was assessed by the primary care nurse responsible for both the mother and baby. Outpatient nursing care was provided on the basis of a contract between our institution and county and private nursing agencies. Nurses making the visits had extensive experience in postpartum maternal and newborn care.

From discharge data compiled by the medical records department at the university hospital of the University of Colorado Health Sciences Center (UCHSC), Denver, maternal age and financial status were obtained for all mothers who delivered infants between July 1, 1984, and Sept 30, 1985. "Sliding scale" data (Colorado State Legislature Indigent Care Program) were used to determine financial status.

Newborn hospital and outpatient medical records were retrospectively reviewed for 2000 consecutively born infants admitted into the transitional nursery for level I care

Table 1.—Criteria for Early Discharge

Delivery is vertex, single, sterile, and vaginal.
Apgar scores at 1 and 5 min are >7.
The infant is term (38 to 42 wk) and weighs 2700 to 4000 g.
Minimum stay of 24 h, transition to normal thermoregulation in an open crib, completion of two successful feedings, evidence of stool and void, completion of neonatal screening for metabolic disease and blood type and Coomb's test (Rh − and O mothers) prior to discharge.
Vital signs within normal ranges at discharge:
Axillary temperature 36.1°C to 37.2°C
Heart rate 110 to 150 beats per minute
Respirations 25/min to 60/min.
The infant has a normal neonatal hospital course and presents no signs or symptoms that require continuous observation.
Blood dextrose concentration maintained >2.5 mmol/L
Hematocrit 0.45 to 0.65
ABO-incompatible infants must be held for 48 hours and released only if they do not require therapy for hemolysis.
Physical examination completed by house officer.
Demonstration of mother's understanding and ability to provide adequate care for her newborn; infant care education provided on a one-to-one or classroom basis by the nursing staff prior to discharge.
Signed documentation by mother that states her obligation to participate in follow-up care.

Accepted for publication Aug 15, 1988.

From the Department of Pediatrics, University of Colorado School of Medicine, and the Lubchenco Center for Perinatal Research, Denver.

Read before the 57th Annual Meeting of the Society for Pediatric Research, May 3, 1988, Washington, DC

Reprint requests to Department of Pediatrics, Container B-195, University of Colorado Health Sciences Center, 4200 E Ninth Ave, Denver, CO 80262 (Dr Rosenberg).

at UCHSC between July 1, 1984, and Sept 30, 1985. Infants who initially required a higher intensity of care (ie, direct admissions into level II or III nursery units) were excluded from the study. The inability of the mother to speak English did not disqualify a child from discharge after less than 36 hours. The data collected included the following: sex, gestational age, birth weight, length of hospital stay, neonatal complications, need to transfer into level II or III units, reason for the hospital stay to exceed 36 hours, documentation of outpatient follow-up within 48 hours of initial discharge, and readmission to the hospital within seven days of initial discharge. Gestational age was recorded as that determined obstetrically unless a discrepancy of greater than two weeks was found compared with a determination by the Ballard scoring system.[6] In those instances, the Ballard gestational age was used. An outpatient follow-up visit was considered successful if there was charted documentation of contact within 48 hours of initial discharge by a county public health nurse, a private visiting nurse organization, or a private practitioner or if there was a documented university hospital pediatric clinic visit.

The results were analyzed for continuous variables by Student's t test and for discrete variables using χ^2 analysis and Fisher's exact test.

RESULTS

Review of the financial status of mothers who delivered infants at the UCHSC from July 1, 1984, through Sept 30, 1985, demonstrated that 77% were in a lower income bracket (23% were eligible for Medicaid assistance, and the remaining 54% had an average income for a family of four <$17 000 per year). The maternal age in this group was 23.2 ± 5.1 years (mean ± SD).

The newborn medical records from the 2000 infants born during the study period were divided into three groups. Group 1 consisted of infants discharged within 24 to 36 hours of birth (n = 1091), group 2 infants were discharged 36 to 48 hours after birth (n = 343), and group 3 infants were discharged more than 48 hours after birth (n = 563). Three records were deleted due to inadequate information. Newborn demographics are summarized in Table 2. Although no significant differences in birth weight and gestational age were found among any of the discharge groups, there was a trend in group 3 toward greater numbers of infants of 37 weeks' gestation or less and 42 weeks' gestation or longer as well as greater numbers of infants small or large for gestational age. The only significant differences among the groups were in the incidence of Apgar scores of 6 or lower at one and five minutes, the frequency of transfer to the level II nursery, and the incidence of hospital readmission within the first week of life.

Table 3 details the reasons hospital stay exceeded 36 hours for group 2 and 3 infants. Maternal problems that included recovery from cesarean section, postpartum tubal ligation, and recovery from pregnancy-induced hypertension and genital injuries (lacerations and contusions of the maternal genitalia) accounted for 31.8% (288/906) of the reasons infants remained hospitalized longer than 36 hours. Low birth weight (small for gestational age and preterm) was the most frequent neonatal cause for the newborn hospitalization to exceed 36 hours (93/906 [10.3%]). The 51

Table 2.—Newborn Demographics

Characteristic	Length of Stay, h		
	24-36	36-48	>48
No. of patients (% of total population)	1091 (54.6)	343 (17.2)	563 (28.2)
Birth weight, g*	3217 ± 13	3215 ± 27	3195 ± 23
Gestational age, wk*	39.7 ± 0.1	39.8 ± 0.3	39.8 ± 0.3
Sex, No. (%)			
M	512 (46.9)	171 (49.9)	293 (52.0)
F	579 (53.1)	172 (50.1)	270 (48.0)
Apgar score, No. (%)			
1 min			
≤6	134 (12.3)	56 (16.3)†	115 (20.4)†
≥7	957 (87.7)	287 (83.7)†	448 (79.6)†
5 min			
≤6	12 (1.1)	4 (1.2)	14 (2.5)†
≥7	1079 (98.9)	339 (98.8)	549 (97.5)†
Admitted to level II nursery, No. (%)	1 (0.09)	8 (2.3)‡	72 (12.8)‡
Readmitted to hospital, No. (%)	25 (2.3)	5 (1.5)	5 (0.89)†

*Values are mean ± SEM.
†$P<.05$ compared with infants hospitalized less than 36 hours by χ^2 test.
‡$P<.05$ compared with infants hospitalized less than 36 hours by Fisher's exact test.

Table 3.—Reason for Length of Stay Greater Than 36 Hours

Reason	Length of Stay (h), No. (%) of Patients		
	36-48	>48	Total
No. of patients	343	563	906
Cesarean section	0	183 (32.5)	183 (20.2)
Maternal	57 (16.6)	48 (8.5)	105 (11.6)
Low birth weight	44 (12.8)	49 (8.7)	93 (10.3)
Jaundice	49 (14.3)	42 (7.5)	91 (10.0)
To rule out infection	24 (7.0)	59 (10.5)	83 (9.2)
Respiratory	19 (5.5)	56 (9.9)	75 (8.3)
Social	26 (7.6)	25 (4.4)	51 (5.6)
Diagnostic evaluation	20 (5.8)	28 (5.0)	48 (5.3)
Large for gestational age	28 (8.2)	16 (2.8)	44 (4.9)
Feeding problems	14 (4.1)	13 (2.3)	27 (3.0)
Polycythemia	4 (1.2)	20 (3.6)	24 (2.6)
Other causes	32 (9.3)	13 (2.3)	45 (5.0)
Undetermined causes	26 (7.6)	11 (2.0)	37 (4.1)

Table 4.—Outpatient Follow-up

Follow-up Visits	No. (%) of Patients With Length of Stay of 24 to 36 h
Successful	994 (91.1)
Unsuccessful	97 (8.9)
No documentation	42 (3.8)
Could not locate	45 (4.1)
Refused by parent	7 (0.6)
Child adopted	3 (0.3)

Table 5.—Reasons for Readmission

Reason	Length of Stay (h), No. (%) of Patients		
	24-36	36-48	>48
No. of patients	25	6	5
Jaundice	15 (60.0)	3 (50.0)	5 (100)
To rule out infection	4 (16.0)	0	0
Social	2 (8.0)	0	0
Maternal	1 (4.0)	1 (16.7)	0
Respiratory	1 (4.0)	1 (16.7)	0
Feeding problems	1 (4.0)	1 (16.7)	0
Circumcision problems	1 (4.0)	0	0

infants who stayed for social reasons included all infants born to mothers with psychiatric disease and substance abuse. A search of both the infants' and mothers' medical records did not reveal a cause for prolonged hospital stay in 4.1% of cases, the majority in group 2 infants. A delay in the writing of a discharge order and a mother awaiting a prescheduled parenting class were considered the most likely causes.

The experience with the mandatory outpatient follow-up visit within 48 hours of discharge for all group 1 infants is presented in Table 4. Successful visits were accomplished in 91.1% of the cases. The overall readmission rate for the entire population studied was 1.8% (36/1997). Significantly greater numbers of readmissions came from infants in group 1 (2.3%) than from group 3 (0.89%, $P<.05$) (Table 2). The reasons for readmission are detailed in Table 5. Treatment of jaundice with phototherapy was the most frequent cause for readmission in all three groups (23/1997 [1.2%]), although 65% (15/23) of these readmissions came from group 1. The second most common reason for readmission was physical signs suggesting bacteremia or viremia (4/36 [11.1%]). No systemic infection was subsequently proved by culture. Nursing follow-up 48 hours after discharge did occur in 24 (96%) of 25 of the infants readmitted from the early discharge group and was instrumental in the recognition and subsequent treatment of their problems.

COMMENT

Guidelines for early discharge have been established by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) and are intended for infants hospitalized no longer than 12 to 24 hours after delivery.[7] These guidelines address both medical and social issues in an attempt to assure a safe early discharge. Delivery must be vaginal and uncomplicated, with a subsequent smooth transition for the infant. Thermal homeostasis and successful feeding must be accomplished, necessary laboratory data reviewed, and maternal skills in newborn care demonstrated prior to discharge. The guidelines also require considerable antenatal planning between family and caretakers as well as participation in educational programs on child care. Furthermore, adequate maternal support systems and postnatal medical follow-up within two to three days of delivery are emphasized.

Illiteracy, young maternal age, lack of transportation, and inability to defray the cost of prenatal care may serve to limit prenatal child care education and medical care for women in lower socioeconomic groups. Single-parent status may limit support at home. Provision of health care through several ambulatory systems as well as frequent household moves and a lack of telephone service compromise the establishment of optimal follow-up in the postpartum period. These problems could serve to limit the applicability of early newborn discharge, as outlined by the AAP and ACOG, to large segments of the population that otherwise meet the medical criteria.

Our study demonstrates that a relatively short newborn stay of 24 to 36 hours is adequate to assure safety for a normally born infant from an indigent population. The readmission rate of 2.3% for the short-stay group, although significantly greater than that experienced by the infants who stayed longer, primarily involved infants with jaundice (60%) or infants about whom there was concern for infection (16%). The data also show that nonmedical early discharge criteria drafted by the AAP and ACOG could be safely modified to accommodate the needs of an indigent population. Furthermore, it was reassuring that follow-up occurred within 48 hours of discharge in 91% of the early-release infants and was instrumental in assessing significant problems within this group.

The six-hour period of transition after birth is when a majority of neonatal problems are manifested.[5,8] Our experience was similar to that reported by Britton et al[5] in that successful completion of the six-hour transition generally assured continued medical stability. However, a hospital stay longer than the minimum six to 12 hours recommended by the AAP and ACOG[7] was necessary in this clinic population to perform the necessary education in child care. This was critical to the success of our program, since it was often impossible to perform this instruction prenatally. Furthermore, the follow-up visit was important in aiding the many mothers with inadequate support structures as well as reinforcing in-hospital teaching.

The medical criteria listed in Table 1 were based on the AAP and ACOG recommendations.[7] We found that our Apgar score criteria were more stringent than necessary. Over 12% of group 1 infants failed to meet the one-minute requirement, while 1.1% failed to meet the five-minute requirement. In no case

did this lead to problems after discharge and/or readmissions. Infants with ABO incompatibility could be safely discharged at 24 to 36 hours if jaundice was not clinically evident, and a 48-hour follow-up visit could be assured.

We were reassured by nursing follow-up that was successful in 91% of all short-stay admissions. However, caution must be exercised for early release in patients with existing problems (eg, jaundice) if follow-up cannot be assured. In our population, despite agreement for outpatient follow-up prior to discharge, follow-up did not occur for 52 patients because families could not be located or refused care. For another 42 families, we could not document whether the visits actually took place.

Our results are similar to those of Pittard et al,[9] who recently reported an overall readmission rate for relatively short-stay newborns from a university hospital population from South Carolina of 3.0% (compared with 2.3% in our study). In contrast, Pittard et al did not show a difference in the readmission rate based on the length of newborn hospitalization, while the present study demonstrated an increased rate (2.3% vs 0.89%) for infants released after less than 36 hours compared with those kept for greater than 48 hours. This difference is likely related to the longer follow-up period evaluated in the study by Pittard et al (six weeks vs one week). This possibility is supported by the high rate of readmission for suspected infection in the South Carolina study. Concern for infection accounted for 68% (2.1% of all early discharges) of the readmissions in the study by Pittard et al compared with 16% in the present study (0.37% of early discharges). The longer period likely included infants with postnatally acquired infections. Indeed, the one-week period used for evaluation of readmission in our study was specifically chosen to discern problems that might have been missed in either the initial nursery stay or the 48-hour follow-up evaluation, while excluding problems of later onset. Readmission rates for neonatal jaundice should not have been affected by the different length of the follow-up period, since most of those readmissions would be expected within one week of birth. In fact, 1.4% of the early discharges in the present study were readmitted for jaundice compared with only 0.2% in the study by Pittard et al. This difference is likely due to the application of stricter discharge criteria in the South Carolina study that did not permit early discharge of "clinically icteric" infants. Our standards for the discharge of icteric infants without hemolytic disease were more liberal because of the assurance of outpatient follow-up.

The rates of prolonged hospitalization were similar in the two studies (45% and 39%). However, differences did exist in the breakdown of causes for prolonged hospitalization. Maternal morbidity and cesarean sections accounted for 57% of the cases in the South Carolina group compared with 31.8% in the current study. Among neonatal problems, infants with low birth weight and those who were large for gestational age accounted for 15.4% of prolonged stays in the current study vs 2.5% in South Carolina. As noted above, jaundice was a more frequent cause for prolonged hospitalization in South Carolina than in Denver (15% vs 10%). It is likely that racial mix, regional practice differences, and selected diagnostic categories in the retrospective reviews contributed to the noted differences.

A relatively short neonatal stay of 24 to 36 hours following a normal term birth and uneventful postnatal course appears to be safe for an indigent population. Care must be taken to provide the mother with adequate in-hospital child care education and suitable follow-up prior to initial discharge.

Funding for statistical analysis was provided by the Lubchenco Center for Perinatal Research, Denver.

We thank Jo Anne Bolton for preparation of the manuscript and Gerald Merenstein, MD, for review of the manuscript.

References

1. Theobald GW: Home on the second day: The Bradford experiment: The combined maternity scheme. *Br Med J* 1959;2:1364-1367.
2. Hellman LM, Kohl SG, Palmer J: Early hospital discharge in obstetrics. *Lancet* 1962;1:227-232.
3. Pritchard JA, MacDonald PC, Gant NF: Obstetrics in broad perspective, in *Williams' Obstetrics*, ed 7. East Norwalk, Conn, Appleton-Century-Crofts, 1985, pp 1-6.
4. Yanover MJ, Jones D, Miller MD: Perinatal care of low-risk mothers and infants: Early discharge with home care. *N Engl J Med* 1976;294:702-705.
5. Britton HL, Britton JR: Efficacy of early newborn discharge in a middle-class population. *AJDC* 1984;138:1041-1046.
6. Ballard JL, Kazmaier K, Driver M: A simplified assessment of gestational age. *Pediatr Res* 1977;11:374.
7. American Academy of Pediatrics, Committee on Fetus and Newborn, American College of Obstetricians and Gynecologists, Committee on Obstetrics: *Guidelines for Perinatal Care*. Elk Grove Village, Ill, American Academy of Pediatrics, 1983, pp 91-92.
8. Desmond MM, Rudolph AJ, Phitaksphraiwan P: The transitional care nursery: A mechanism for preventive medicine in the newborn. *Pediatr Clin North Am* 1966;13:651-668.
9. Pittard WB III, Geddes K: Newborn hospitalization: A closer look. *J Pediatr* 1988;112:257-261.

In Other AMA Journals

JAMA
Hospital Behavior Under Competition and Cost-Containment Policies
G. A. Melnick, J. Zwanziger (*JAMA* 1988;260:2669)

The Diagnosis of Group A, β-Hemolytic Streptococcal Pharyngitis in the Office Setting

Rapid Latex Test vs Throat Culture

Bruce Taubman, MD; Robert P. Barroway, MD; Karin L. McGowan, PhD

• We compared a rapid latex agglutination test with cultures of throat specimens to diagnose group A β-hemolytic streptococcal pharyngitis in an office setting. The throat cultures were interpreted by two pediatricians independently and evaluated by a reference laboratory. Five hundred seventy-two children participated in the study. The latex agglutination test had a sensitivity of 89.4% and a specificity of 85.7%. Cultures of throat specimens obtained in the office had a sensitivity of 91.9% and a specificity of 91.7% when interpreted by investigator 1, and a sensitivity of 90.0% and a specificity of 95.1% when interpreted by investigator 2. There was no statistically significant difference between the numbers of false-negative results generated by the two procedures. We conclude that although somewhat less specific, the latex test is as sensitive as cultures of throat specimens in the office setting.

(*AJDC* 1989;143:102-104)

The development of latex agglutination assays for group A streptococcal antigen has resulted in the production of numerous office kits that offer the physician a rapid method for diagnosing streptococcal pharyngitis. Several studies have been conducted comparing the accuracy of latex agglutination tests with that of the conventional cultures of throat specimens in diagnosing group A streptococcal pharyngitis in children.[1-4] These studies have used microbiology reference laboratories to process and interpret the results of the throat cultures. The sensitivity of the latex agglutination tests in these studies has ranged from 65% to 95%. These levels of sensitivity have raised legitimate concerns that routine use of a latex agglutination test in the pediatric office would lead to a significant underdiagnosis of children with group A streptococcal pharyngitis.[5] Given the recent increase in the incidence of acute rheumatic fever, it is more important than ever that correct diagnosis of streptococcal pharyngitis be made and appropriate treatment offered to children.[6,7]

For the pediatrician to decide between cultures incubated and interpreted in the office and performance of a latex agglutination test, comparison of the sensitivities of the two tests under similar office conditions must be known. We are aware of only one study to date that attempted such a comparison. Roddey et al[8] found processing and interpreting cultures of throat specimens in the office to be more sensitive than latex agglutination testing; the sensitivity of throat cultures was 92%, compared with 77% for latex testing. However, the low sensitivity of the latex agglutination test in their study raises questions about the technique and experience of those performing the test.

Two of the investigators in this study are practicing pediatricians with more than ten years of experience performing and reading cultures of throat specimens and three years of experience in the use of latex agglutination testing. Therefore, we undertook a study comparing the accuracy of the two methods when performed in our office setting.

PATIENTS AND METHODS

Children between ages 2 and 18 years (mean, 8 years) seen in two of the authors' private practice (B.T. and R.P.B.) between Oct 20, 1986, and March 31, 1987, for the diagnosis of group A β-hemolytic streptococcal (GABHS) pharyngitis were considered for the study group. In all cases, parents were asked to consent to their child's participation in the study. The children were examined and the severity of pharyngitis and adenopathy, as well as the presence or absence of fever (temperature ≥38.3°C), exudate, and scarlet rash, were recorded. Two separate throat swabs were obtained from each patient after consent was obtained. Each throat swab was obtained by rubbing a dacron-tipped swab over the posterior pharynx and both tonsils or tonsillar fossae. The first throat swab taken was immediately processed with a latex agglutination strep test (Culturette, Marion Scientific Corp, Kansas City, Mo) following the manufacturer's instructions.

The second swab was immediately streaked onto one third of a 5% sheep's blood agar plate. Secondary streaking was done with a wire loop that had been heated to incandescence and cooled. A 0.04-U bacitracin disc (BBL Microbiology Systems, Cockeysville, Md) was placed on the agar at the transition between the initial inoculation and the secondary streaking. The agar plate was coded and placed in an incubator at 37°C for 18 to 24 hours. The blood agar plates were examined for GABHS independently by the two physicians. Both physicians were blind to the plate code and therefore did not know the results of the latex test when the plates were examined. Also, each physician interpreting the blood agar plates was blind to the results of the other's interpretation. The plates were refrigerated at 4°C until being transported to the Children's Hospital of Philadelphia microbiology laboratory. There, plates were examined and β-hemolytic streptococci were identified by colony morphology, Gram's stain morphologic features, and negative catalase reaction. β-Hemolytic streptococci were grouped using a latex-bound antibody test (Streptex, Wellcome Reagents, Ltd, Beckenham, England). The reference laboratory was blind to the results of both office tests until completion of the study. The laboratory culture was considered to be the reference with which all other study results, both latex and office culture, were compared.

The results of latex testing and office cultures were compared at the end of the study. Statistical analysis included Fisher's exact test, calculation of χ^2, and determination of sensitivity, specificity, positive predictive value, and negative predictive value for both office tests.

Accepted for publication Sept 26, 1988.

From the Department of Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia (Drs Taubman and McGowan), and Cherry Hill (NJ) Pediatric Group (Drs Taubman and Barroway).

Reprint requests to Cherry Hill Pediatric Group, 600 W Marlton Pike, Cherry Hill, NJ 08002 (Dr Taubman).

Table 1.—Comparison of Office Latex Test With Reference Laboratory Culture

	Reference Culture Results		
	No. Positive	No. Negative	Total
Office latex test results			
No. positive	143	59	**202**
No. negative	17	353	**370**
Total	**160**	**412**	**572**

Table 2.—Comparison of Reference Laboratory Culture With Office Culture (Investigator 1)

	Reference Culture Results		
	No. Positive	No. Negative	Total
Office culture results			
No. positive	147	34	**181**
No. negative	13	378	**391**
Total	**160**	**412**	**572**

Table 3.—Comparison of Reference Laboratory Culture With Office Culture (Investigator 2)

	Reference Culture Results		
	No. Positive	No. Negative	Total
Office culture results			
No. positive	144	20	**164**
No. negative	16	392	**408**
Total	**160**	**412**	**572**

RESULTS

Throat swabs were obtained from 572 children in this study. There were only five children considered for the study from whom parental consent was not obtained. Of the total, 160 (28%) were found to be positive for GABHS by the reference laboratory. Table 1 compares the results of the office latex test with the culture results obtained at the reference laboratory. The office latex test had a sensitivity of 89.4% and a specificity of 85.7% and the percent of false-negative results was 3.0%. The predictive value positive of the office latex test was 70.8% and the negative predictive value was 95.4%.

Tables 2 and 3 compare the results of office cultures as interpreted by the two pediatricians with the results of the cultures read by the reference laboratory. When interpreted by investigator 1, office cultures had a sensitivity of 91.9%, specificity of 91.7%, positive predictive value of 81.2%, negative predictive value of 96.7%, and percent of false-negative results of 2.3%. When interpreted by investigator 2, office cultures had a sensitivity of 90.0%, specificity of 95.1%, positive predictive value of 87.8%, negative predictive value of 96.1%, and percent of false-negative results of 2.8%. As seen in Tables 2 and 3, investigator 1 was more likely to interpret a culture as positive than was investigator 2 (31.6% vs 28.7%), by a statistically significant difference. Of the 21 cultures for which the two pediatricians found different results, investigator 1 found 19 to be positive, while investigator 2 found only two to be positive. The difference in positive culture results between investigator 1 and the reference laboratory, 3.7%, was found to be statistically significant. This was not the case with investigator 2, for whom the difference was only 0.7%.

Of the 17 cases in which the latex test gave a false-negative result, the office culture would have identified seven cases correctly when interpreted by investigator 1 and five cases correctly when interpreted by investigator 2. This would decrease the percent of false-negative results to 1.7% and 2.1%, respectively. This percentage of false-negative results was not statistically different from that obtained with the office latex test (3.0%).

Clinical signs were shown to be poor indicators of GABHS pharyngitis. In fact, no combination of all five clinical signs could be shown to be helpful. The percent of agreement between the presence of GABHS and fever (temperature ≥38.3°C) was only 55.8%, and only 57% of all children judged to have severe pharyngitis were shown to have a positive culture. The figures for the presence of exudate and rash were slightly better. There was a 72.4% agreement between the presence of exudate and GABHS and a 73.9% agreement between the presence of scarlet rash and GABHS. Unfortunately, so few children were found with positive symptoms of exudate (n = 17) and rash (n = 15) that we concluded that these two signs would not often be helpful.

COMMENT

Because rapid diagnostic procedures are now available, many pediatricians are considering alternative approaches to culturing throat specimens for detecting GABHS pharyngitis. Many investigators have attempted to determine whether rapid latex tests are as sensitive and specific as traditional techniques. Most of these studies have compared rapid tests for GABHS pharyngitis with cultures of throat specimens performed in large diagnostic microbiology laboratories or in university hospital settings.[1-4] Numerous studies have shown, however, that office-based cultures have variable agreement with cultures from microbiology laboratories and that the results depend entirely on the experience of the individual physicians.[9,10] Thus, comparative studies in which culture results were obtained using the services of a microbiology reference laboratory may not necessarily be applicable to an office practice. Many physicians perform cultures of throat specimens in their offices rather than sending samples to a reference laboratory. Numerous experts have recommended office throat culturing as a simple, inexpensive, and reliable procedure.[4,8] A potential for significant error, however, exists, even with the traditional office culture. False-negative culture results can occur for a variety of reasons: poor specimen collection, delay in culturing, use of outdated media, inadequate incubator temperature control, overgrowth of other bacteria, and errors due to inexperience on the part of personnel who are examining culture plates. It has been shown that the accuracy rate appears to be higher for physicians who have received some kind of training in interpreting cultures.[11,12] The physicians involved in this study had received training in culture interpretation and had used throat cultures to diagnose GABHS pharyngitis in their office practice for more than ten years. Despite this, there was still a significant difference between the two investigators' interpretations of culture results. Investigator 1 was more likely to misinterpret negative cultures as positive (due to other β-hemolytic organisms) and was less likely to call positive cul-

tures negative, further illustrating the subjective aspect of evaluation of office cultures.

Physicians continue to be deluged with a wide variety of rapid tests that are available to detect GABHS directly from throat swabs. These tests are easy to perform, but for most physicians, the issue should be whether the quality of the rapid test is sufficient to replace the methods they are presently using to detect GABHS in their office practice. Pediatric populations offer the greatest challenge when evaluating these rapid tests because the positivity rate is much higher than with adults, most patients are under age 13 years, making adequate specimen collection difficult, and most pediatricians consider any numbers of GABHS found on culture to be significant. All these factors have the overall effect of lowering test sensitivity.

Our results with the latex agglutination strep test compare favorably with those of previous studies performed with children. The sensitivity of the latex test in this study was 89.4%, while of four previous studies, it was 88% in two, 90% in one, and 83% in a fourth.[1-4] The sensitivity results of the office cultures were not statistically different than those of the latex test. Office cultures interpreted by one investigator had a sensitivity of 91.7%; when interpreted by the second investigator, the sensitivity was 90%. In evaluating the reliability of the latex test, of utmost importance is the number of children with GABHS pharyngitis that would be missed by the latex test, ie, children who potentially could go on to develop sequelae. The percent of false-negative results that occurred with the office test was 2.7% (17 patients). Of the 12 office throat cultures that were misinterpreted as negative by both physicians, four were mixed cultures with *Staphylococcus aureus* in which only the *S aureus* was noted by the physicians, three were the result of nonreactive bacitracin discs, and one was heavily overgrown with a gram-negative rod. The remaining four cultures each had less than 50 colonies of GABHS, which were detected by the reference laboratory because additional subcultures were performed from the primary blood agar plate.

The specificity of the latex agglutination test in this study (86%) was lower than expected. Most published reports show these tests to be quite specific (88% to 100%) but to vary considerably in sensitivity. One reason for lower specificity may be due to possible interference from over-the-counter cold medications. Such medications have been shown to cause false-positive results with this particular latex test.[13] In this study, parents were not asked if they had given their child any type of medication prior to the office visit. Another reason for a lower level of specificity may be due to overinterpretation of the test results, since both physicians were aware of the clinical status of the patients.

We are aware of only one other study that attempted to compare a latex agglutination test performed in the office with cultures of throat specimens processed in the same office. Roddey et al[8] obtained a sensitivity of 92%, similar to our results. The sensitivity of the office latex test in their study, however, was only 77%, which is significantly lower than that found in the present study as well as in previous studies. The only discernible difference in methodology between our study and that of Roddey et al is the method by which throat specimens were obtained. In their study, two swabs were taken simultaneously. One swab was then used for the latex test and the other for culture. Since other investigators have used the double swab technique with much better sensitivity results than those of Roddey et al, it is more likely that the difference in sensitivity of the latex test between this study and theirs lies in the difference in the experience of the people performing the latex test.

Some physicians who have felt that the sensitivity of the latex test is not adequate have suggested using the latex agglutination test as a screen and then performing cultures of throat specimens on children who are latex test–negative.[4,8] The sensitivity of this procedure during the period of the study would have been 93.7% and 92.5% for each of the two investigators. This would translate to one investigator correctly diagnosing seven of the 17 cases and the second investigator correctly diagnosing five of the 17 cases of GABHS pharyngitis that would have been missed had the latex test been used alone. This improvement is not statistically significant. Whether the improvement is clinically significant enough to justify the use of both test procedures is a decision that each practitioner must make.

SUMMARY

We found the latex agglutination strep identification test to be as sensitive as cultures of throat specimens in diagnosing GABHS pharyngitis when both procedures were performed by experienced pediatricians. The percent of false-negative results of the latex test was not significantly higher than that found with office cultures and we believe these results to be well within clinically acceptable limits. In our hands, the quality of the rapid test is sufficient to replace the culture procedure we were previously using. Since the latex test is convenient to perform, is preferred by parents, and yields same-day results, we have chosen to use it routinely in our office.

References

1. Gerber MA, Spadaccini LJ, Wright LL, et al: Latex agglutination test for rapid identification of group A streptococci directly from throat swabs. *J Pediatr* 1984;105:702-705.

2. Chang MJ, Mohla C: Ten-minute detection of group A streptococci in pediatric throat swabs. *J Clin Microbiol* 1985;21:258-259.

3. Berkowitz CD, Anthony BF, Kaplan EL, et al: Cooperative study of latex agglutination to identify group A streptococcal antigen on throat swabs in patients with acute pharyngitis. *J Pediatr* 1985;107:89-92.

4. Gerber MA, Randolph MF, Chantry J, et al: Antigen detection test for streptococcal pharyngitis: Evaluation of sensitivity with respect to true infections. *J Pediatr* 1986;108:654-658.

5. Gerber MA: Culturing of throat swabs: End of an era? *J Pediatr* 1985;107:85-88.

6. Hosier DM, Gruenen JM, Teske DW, et al: Resurgence of acute rheumatic fever. *AJDC* 1987;141:730-732.

7. Versy LG, Wiedmeier SE, Orsmond GS, et al: Resurgence of acute rheumatic fever in the intermountain area of the United States. *N Engl J Med* 1987;316:425-427.

8. Roddey OF, Clegg HW, Lizabeth TC, et al: Comparison of a latex agglutination test and four culture methods for identification of group A streptococci in a pediatric office laboratory. *J Pediatr* 1985;108:347-352.

9. Battle CU, Glasgow LA: Reliability of bacteriologic identification of beta hemolytic streptococci in private offices. *AJDC* 1971;122:134-136.

10. Morris DS: Reliability of office based diagnostic tools in streptococcal pharyngitis. *W Va Med J* 1984;80:89-94.

11. Larsson P, Lind L: The need for control of throat streptococcal cultures in general practice. *Scand J Infect Dis* 1983;suppl 39:79-82.

12. Tucker JB, Barasz D, Greenfield S, et al: Throat culturing techniques in the family practice model unit. *J Fam Pract* 1981;12:925-931.

13. Uhlik DJ: Rapid diagnosis of streptococcal pharyngitis. *Am Clin Prod Rev* 1985;9:36-43.

Failure of Electrocardiographic Monitoring to Detect Cardiac Arrest in Patients With Pacemakers

John R. Brownlee, MD; Gerald A. Serwer, MD; Macdonald Dick II, MD;
Thomas Bauld, PhD; Amnon Rosenthal, MD

• Two children with cardiac pacemakers are described who experienced cardiorespiratory arrest not detected by the electrocardiographic (ECG) monitor. The pacemaker stimuli were interpreted by the monitor as a QRS complex with inhibition of the heart rate alarm, demonstrating the need for reliable non-ECG monitoring in patients with pacemakers. A review of all deaths in children with pacemakers in the last ten years also shows the high association of respiratory failure in patients with congenital heart disease and a pacemaker, underscoring this need. Various non-ECG monitoring modalities are discussed. Finally, analysis of the ECG monitor characteristics contributing to inappropriate sensing of the pacemaker stimulus was performed, showing the direct relation between the pacemaker stimulus amplitude seen by the monitor and the monitor sensitivity with inappropriate sensing, and the inverse relation between the monitor bandwidth and inappropriate sensing. Recommendations for monitor adjustment when monitoring patients with pacemakers are provided.

(*AJDC* 1989;143:105-107)

Use of pacemakers is an important therapeutic modality for children with life-threatening bradyarrhythmias. Most pediatric patients requiring pacemaker implantation have structural cardiac disease and have undergone prior cardiac surgery.[1] This fact, together with the need for periodic pacemaker system revision, increases the expectation that physiologic monitoring will be needed. Since heart rate in such children is determined by pacemaker settings, heart rate monitoring alone is not sensitive to changes in the child's clinical state as in the child with normal conduction.[2] In addition, the ability of the electrocardiographic (ECG) monitor to distinguish between the pacemaker stimulus and the true QRS complex is influenced by many factors. If both the pacemaker stimulus artifact and the QRS complex are sensed, the monitor may continue to count the pacemaker artifact in the presence of lack of capture with no QRS or bradycardia, not triggering the heart rate alarm. Despite the use of state-of-the-art monitors with functioning detection, filtering, and alarm systems, two children experienced cardiac arrests not detected by their ECG monitors. A review of all deaths in children who had undergone pacemaker implantation at our institution in the last decade further underscores this need by demonstrating the high incidence of respiratory failure in children with congenital heart disease who are likely to be pacemaker dependent. This report details these two cases, reviews all recent deaths in children with pacemakers, and analyzes factors affecting ECG monitor sensing of the pacemaker stimulus.

Accepted for publication Oct 12, 1988.

From the Division of Pediatric Cardiology, Department of Pediatrics (Drs Brownlee, Serwer, Dick, and Rosenthal), and the Department of Biomedical Engineering (Dr Bauld), C. S. Mott Children's Hospital, University of Michigan, Ann Arbor.

Reprint requests to F1615, Box 0204, C. S. Mott Children's Hospital, University of Michigan Medical Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109 (Dr Serwer).

PATIENT REPORTS

PATIENT 1.—A 14-month-old girl who had undergone cardiac transplantation at age 7 months for inoperable complex cyanotic congenital heart disease was admitted with mild respiratory distress and low-grade fever. Shortly following transplantation, she required insertion of a permanent pacemaker because of complete heart block associated with an episode of rejection.

On admission, a presumed diagnosis of rejection was made. The patient was monitored by an ECG monitor and hourly determination of vital signs in a moderate-care area. Five minutes after vital signs were determined, the patient was found blue, limp, apneic, and pulseless. The cardiac monitor showed pacing spikes at a rate of 90 per minute without QRS complexes, but the monitor alarm was not triggered. The pacing artifacts were being interpreted by the monitor as normal cardiac electrical activity. Cardiopulmonary resuscitation was successful.

PATIENT 2.—A 1-year-old girl with pulmonary atresia and a ventricular septal defect had a pacemaker implanted for surgically induced complete heart block following complete repair of her cardiac defect. Her postoperative course was complicated by repeated episodes of bronchospasm requiring aminophylline therapy. While she was being monitored by both ECG and respiratory impedance monitor in an intermediate-care area, frequent false alarms prompted her mother to turn off the respiratory monitor alarm and later leave the room. Several minutes later the child was discovered to be in cardiopulmonary arrest. The ECG monitor was displaying the pacing spikes but the alarm was not triggered, again due to the pacing spikes being interpreted as QRS complexes. Resuscitation attempts were unsuccessful. Necropsy revealed severe acute aspiration pneumonitis.

REVIEW OF DEATHS IN CHILDREN WITH PACEMAKERS

To determine the incidence of respiratory-related deaths in children with pacemakers, the records of all children dying following pacemaker implantation at our institution between January 1978 and January 1987 were reviewed and 12 patients were identified; all but one had structural heart disease (Table). Their ages at the time of death ranged from 19 days to 17 years, five children being under age 15 months and seven children being over age 10 years. There were three out-of-hospital unexplained deaths and nine in-hospital deaths. Of the nine in-hospital deaths, five (56%) exhibited respiratory failure

Children With Pacemakers Who Died Between January 1978 and January 1987

Patient No.	Age at Death	Diagnoses	Cause of Death
1	15 mo	Pulmonary atresia with ventricular septal defect; surgical heart block	Respiratory failure from aspiration pneumonitis
2	12 mo	Double-outlet right ventricle with pulmonic stenosis; congenital heart block	Respiratory failure from congestive heart failure
3	5 mo	Total anomalous pulmonary venous return, postoperative, sick sinus syndrome	Respiratory failure from congestive heart failure
4	17 y	Tetralogy of Fallot; surgical heart block	Respiratory failure
5	19 d	Atrioventricular septal defect with aortic hypoplasia; congenital heart block	Respiratory failure from congestive heart failure
6	10 y	D-transposition of great arteries with ventricular septal defect; surgical heart block	Unknown (not in hospital)
7	12 y	Tetralogy of Fallot; sick sinus syndrome	Unknown (not in hospital)
8	17 y	Single ventricle with L-transposition of the great arteries; surgical heart block	Unknown (not in hospital)
9	1 mo	L-transposition of the great arteries with hypoplasia of the right ventricle; congenital heart block	Ventricular arrhythmia
10	14 mo	Restrictive cardiomyopathy; sick sinus syndrome	Ventricular arrhythmia
11	17 y	Atrioventricular septal defect, congenital heart block	Bacterial endocarditis
12	17 y	Tetralogy of Fallot; surgical heart block	Intraoperative

as evidenced by hypercapnia and increasing hypoxia. Four of these five were children under 2 years of age.

FACTORS INFLUENCING ECG MONITOR DETECTION OF PACEMAKER STIMULI

To determine characteristics that may influence detection of a pacemaker stimulus by an ECG monitor, ECG monitors used during the period when the two patients described herein experienced their respiratory arrests were evaluated. An ECG simulator (311A, Fogg Systems, Aurora, Colo) and an external adjustable pacemaker (5330, Medtronic, Inc, Minneapolis) were simultaneously attached to the test monitor. The ECG simulator was set at a rate of 120 beats per minute and an amplitude of 1 mV. The pacemaker was set at a rate of 150 beats per minute. The slew rate was fixed at 700 V/s and pulse width was fixed at 0.8 ms. The pacemaker stimulus amplitude, the ECG monitor filter settings, and the ECG monitor sensitivity were sequentially varied. Monitor settings at which the monitor interpreted the pacemaker stimuli as QRS complexes shown by an increase in the perceived heart rate and at which only true QRS complexes were sensed (pacemaker stimuli were ignored) were determined. This demonstrated that the likelihood of the monitor interpreting the pacemaker stimuli as QRS complexes, thus inhibiting the alarm, was directly related to the pacemaker stimulus amplitude and the monitor sensitivity, and inversely related to the monitor bandwidth. The greater the amplitude of the pacemaker stimulus was, the greater was the sensitivity of the monitor, and the narrower and lower the bandwidth of the monitor was, the more likely was the monitor to interpret the pacemaker stimulus as a QRS complex and inhibit the alarm. Narrow low-frequency bandwidths of 0.5 to 40 Hz were associated with oversensing of the pacemaker stimuli at all amplitudes as measured by the monitor from 15 to 20 mV and all monitor sensitivity settings.

Based on these findings, we make the following recommendations: (1) ECG electrode placement should be such as to maximize QRS amplitude and minimize pacemaker stimulus amplitude; (2) ECG monitor sensitivity should be set just high enough to sense the intrinsic QRS complexes; and (3) ECG monitor filter settings, when adjustable, should be adjusted to keep the bandwidth broad.

COMMENT

The two children described, the frequent presence of respiratory failure in children with congenital heart disease and implanted pacemakers, and the variability of ECG monitor design and settings underscore the need for reliable multimodality monitoring. In the two patients described, cardiac arrest was presumed secondary to respiratory failure as both children had documented respiratory compromise. Acute hypercapnia has been shown to cause an initial increase in heart rate followed by bradycardia.[3] Even though such findings are difficult to apply to the clinical setting, heart rate changes do accompany changes in the clinical state.[2] No such change in our patients' heart rates occurred, owing to the heart rates being determined solely by the pacemaker. Progressive respiratory acidosis and hypoxemia led to loss of cardiac mechanical activity and arrest ensued. Loss of capture was masked by the monitor sensing the pacemaker stimuli and failing to trigger the alarm. The frequent association of respiratory failure with death in pacemaker-dependent children emphasizes the importance of using non-ECG monitoring when these patients are hospitalized.

Analysis of the interaction of the ECG monitor and the pacemaker indicates that close attention to monitor settings is necessary in patients with pacemakers. Careful electrode placement must be employed to maximize the amplitude of the recorded QRS complex while minimizing the recorded pacemaker stimulus amplitude, permitting lower monitor sensitivity settings. Furthermore, attention to the bandwidth of the monitor is necessary to avoid distorting the pacemaker signal into a stimulation of the QRS complex. If monitor filters are user adjustable, the low frequency setting should be as low as possible, with

the high frequency setting as high as practical to maximize bandwidth.

Currently there are multiple methods for non-ECG patient monitoring. Respiratory impedance monitoring is, theoretically, the most appropriate choice to detect apnea or tachypnea, which may accompany cardiorespiratory failure and arrest.[4] However, the technique is limited because of its oversensitivity to nonrespiratory patient movement and lack of information provided about respiratory function.

Transcutaneous oxygen pressure and carbon dioxide pressure monitoring is useful in following a patient's oxygenation and ventilator status. These monitoring methods are widely used in the neonatal period and, if properly correlated with measurement of blood gases, can be useful in older children.[5] However, nonsedated children may not tolerate the irritation of the heat produced by the sensor on the skin.

The pulse oximeter gives an accurate noninvasive assessment of the patient's oxygen saturation and peripheral perfusion.[6,7] It also provides a nonelectrical assessment of the patient's heart rate. Incipient respiratory failure is manifested by a decrease in blood oxygen saturation. However, in an active patient, care must be taken to maintain the sensor's position on the selected extremity to prevent a false alarm secondary to movement.

When monitoring a patient at risk for respiratory failure who is dependent on a cardiac pacemaker, multimodality monitoring is advantageous. All non-ECG monitoring modalities have potential limitations and the most appropriate one should be chosen for the individual patient in addition to ECG monitoring. Careful attention must also be paid to monitoring electrode position and the ECG monitor settings essential to proper recording of the QRS, not the pacemaker artifact. The presence of a cardiac pacemaker in the patient with potential respiratory failure increases the complexity of patient monitoring and must be taken into account when decisions concerning physiologic monitoring are made.

References

1. Serwer GA, Mericle JM: Evaluation of pacemaker pulse generator and patient longevity in patients aged 1 day to 20 years. *Am J Cardiol* 1987;59:824-827.
2. Levin DL, Morriss FC, Moore GC (eds): *A Practical Guide to Pediatric Intensive Care*, ed 2. St Louis, CV Mosby Co, 1984, pp 474-478.
3. Adachi H, Strauss W, Ochi H, et al: The effect of hypoxia on the regional distribution of cardiac output in the dog. *Circ Res* 1976;39:314-319.
4. Farman JV, Juett DA: Impedance spirometry in clinical monitoring. *Br Med J* 1967;4:27-29.
5. Gidding SS, Rosenthal A, Moorehead C: Transcutaneous oxygen monitoring: Its use in the treatment of outpatients with congenital heart disease. *AJDC* 1985;139:288-291.
6. Jennis MS, Peabody JL: Pulse oximetry: An alternative method for the assessment of oxygenation in newborn infants. *Pediatrics* 1987;79:524-528.
7. Fanconi S, Doherty P, Edmends JF, et al: Pulse oximetry in pediatric intensive care: Comparison with measured saturations and transcutaneous oxygen tension. *J Pediatr* 1985;107:362-366.

Book Review

Pediatric Cerebrovascular Disorders, by E. S. Roach and A. R. Riela, 267 pp, $45, Mount Kisco, NY, Futura Publishing, 1988.

This monograph is the first of its kind devoted entirely to cerebrovascular disorders in infants and children. Early in the text, the authors contrast the diversity of cerebrovascular conditions in children with adults. Accordingly, the text includes both an etiologic approach to diagnosis as well as management issues.

Overall, the monograph is comprehensive in scope, well written, and succinct. Numerous pictorial diagrams, figures of computed tomographic and magnetic resonance imaging scans, and arteriograms complement the text. Ample references are also included.

The first chapter gives an introduction and overview of the treatise, providing definitions and risk factors for cerebrovascular disease in children. The ontogeny of the cerebral arterial and venous systems and the distinctive clinical presentations of acute occlusion of these major vessels are reviewed in Chapters 2 and 3. Chapters 4 through 12 cover etiologic aspects of cerebral embolism, hematologic disorders and neoplasms, vasculitis, systemic disorders, aneurysms, and vascular malformations. Chapters 12 and 13 are devoted to traumatic and perinatal cerebrovascular disorders, respectively, while the final chapter reviews migraine.

The authors have written a book that is detailed enough to serve as a selected reference text for individual topics. In addition, it can double as a readable and comprehensive review of all aspects of cerebrovascular disease in children. It should prove worthwhile to pediatric neurologists, in particular, and to other physicians interested in vascular diseases affecting the developing brain of infants and children.

ROBERT C. VANNUCCI, MD
Milton Hershey Medical Center
Hershey, PA 17033

Single Umbilical Artery

A Report of 159 Cases

Alexander K. C. Leung, MBBS, FRCPC, MRCP(UK), MRCPI,
William Lane M. Robson, MD, FRCPC

• We retrospectively reviewed the records of 56 919 infants born from 1966 through 1986 to determine the incidence, significance, and possible associations of single umbilical artery (SUA). One hundred fifty-nine infants were affected. The sex distribution was approximately equal. Fourteen infants (8.8%) were twins who were discordant for SUA. The smallest twin was the one affected in all but two cases. Of the 159 infants, 16 were stillborn and 19 died neonatally. The mean birth weight of all infants with SUA was 2.47 kg, and the mean gestational age was 35.9 weeks. Young primipara and older multipara mothers were more commonly affected. There was an increased incidence of SUA associated with maternal diabetes, epilepsy, toxemia, antepartum hemorrhage, hydramnios, and oligohydramnios. Twenty-six (16.4%) of the associated placentas had anomalies. Seventy-one infants (44.7%) had other congenital malformations. The presence of these malformations was associated with increased mortality. Screening for renal anomalies with ultrasonography or intravenous pyelography was performed in 27 patients and yielded positive results in five (18.5%). We recommend that renal ultrasonography be performed on all infants with SUA.

(*AJDC* 1989;143:108-111)

The umbilical cord of the human newborn normally consists of two arteries and one vein embedded in the jelly of Wharton. The absence of one umbilical artery has been observed since the time of the Renaissance. Vesalius[1] (1543), Fallopio[2] (1561), and Bauhin[3] (1621) have been credited with early references to this condition.

The significance of a single umbilical artery (SUA) was not recognized until 1955, when Benirschke and Brown[4] published a retrospective study of 55 patients with SUA and found that 27 had associated congenital malformations. Their study represented a highly selected population chosen based on the presence of significant pathologic problems. The reported incidence of SUA as well as the frequency and type of associated congenital malformations vary widely. Several explanations could account for this variability. Previously reported prospective studies involved relatively small numbers of patients, and retrospective studies were often based on autopsy material that may not be applicable to the live infant population. The etiology of SUA is not clear.

We retrospectively reviewed hospital records of infants born at the Foothills Provincial Hospital, Calgary, Alberta, in the 21 years from 1966 through 1986 to determine the incidence, significance, and possible associations of SUA.

PATIENTS AND METHODS

From July 1966 through December 1986, 56 919 (29 259 male and 27 660 female) infants were born at the Foothills Provincial Hospital. Ninety-two percent of these infants were white, 5% were Asian, 2% were Indian, and 1% were black. One hundred fifty-nine infants were found to have an SUA. This was confirmed by gross and histologic examination of the placenta. The charts of these 159 infants were reviewed. Particular attention was paid to the race, sex, gestation, Apgar scores, birth weight, associated congenital malformations, family history of SUA, and placental anomalies as well as maternal age,

Table 1.—Birth Weight of Infants With SUA*

Birth Weight, kg	Infants With SUA, No. (%)	Controls, No. (%)
<0.75	9 (5.66)	403 (0.71)
0.75-1.0	5 (3.14)	420 (0.74)
1.0-1.5	13 (8.18)	920 (1.62)
1.5-2.5	66 (41.51)	3786 (6.67)
2.5-4.0	64 (40.25)	45 657 (80.44)
>4.0	2 (1.26)	5574 (9.82)
Total	**159 (100)**	**56 760 (100)**

*SUA indicates single umbilical artery.

Table 2.—Gestational Age of Infants With SUA*

Gestational Age, wk	Infants With SUA, No. (%)	Controls, No. (%)
<30	14 (8.81)	1465 (2.58)
30-34	28 (17.61)	2532 (4.46)
35-37	33 (20.75)	5199 (9.16)
38-41	71 (44.65)	41 298 (72.76)
>41	13 (8.18)	6266 (11.04)
Total	**159 (100)**	**56 760 (100)**

*SUA indicates single umbilical artery.

Accepted for publication Aug 22, 1988.

From the Department of Pediatrics, Alberta Children's Hospital, University of Calgary.

Read before the 65th Annual Meeting of the Canadian Paediatric Society, Calgary, Alberta, July 6, 1988.

Reprint requests to Alberta Children's Hospital, 1820 Richmond Rd SW, Calgary, Alberta, Canada T2T 5C7 (Dr Leung).

parity, gravidity, last menstrual period (LMP), and health. Data for the infants without SUA born at the Foothills Provincial Hospital during the same period of time were used as controls.

RESULTS

There were 159 infants with SUA confirmed by histologic examination of the placenta in 56 919 consecutive deliveries. The incidence of this lesion was one (0.28%) in 358. One hundred forty-six infants (91.8%) were white, eight (5%) were Chinese, one (0.6%) was Korean, one (0.6%) was black, and three (1.9%) were Indian (two West Indian and one East Indian). For mixed marriages, the race of the mother was taken as the race of the infant. There were 78 male and 81 female infants in the study. Fourteen infants (8.8%) were twins. The overall incidence of twin pregnancy in the control group was 1.7%. All of the 14 twins were discordant for SUA. The smaller twin was the one with SUA in all but two cases. The mean birth weights of the twins with and without SUA were 1.73 kg and 2.28 kg, respectively. There were two siblings in this study.

Of the 159 infants, 16 were stillborn and 19 died neonatally, giving a perinatal mortality rate of 22%. The perinatal mortality rate of the control group was 1.9%. Two additional infants with SUA died in the first year of life. The birth weights and gestational ages of infants with SUA are shown in Tables 1 and 2. The mean birth weight was 2.47 kg, and the mean gestational age was 35.9 weeks.

One hundred twenty-five infants (78.6%) were delivered vaginally, while the remaining 34 infants (21.4%) were delivered by cesarean section. In the control group, 82.8% of infants were delivered vaginally, and 17.2% of infants were delivered by cesarean section. Excluding the 16 stillbirths, the mean Apgar scores were 6 at one minute and 8 at five minutes.

The ages of the mothers whose infants had SUA ranged from 17 to 44 years, with a mean of 27.1 years. The mean gravidity and parity of the mothers were 2.2 and 1.8, respectively. Table 3 shows the distribution of infants with SUA according to maternal age and parity; of mothers of infants with SUA, 6.29% were primipara under 20 years of age, and 1.26% were multipara over 40 years of age. The corresponding figures in the control series were 4.74% and 0.32%. Table 4 shows the distribution of infants with SUA according to the month of the LMP of the mother. Five mothers had diabetes mellitus, and two were treated with insulin. Two mothers had epilepsy and were treated with phenytoin (Dilantin) and phenobarbital. Both infants of these epileptic mothers had features of the fetal dilantin syndrome. One mother had hypothyroidism and was treated with levothyroxine sodium. One mother and her infant both had Ehlers-Danlos syndrome. One mother had malignant hyperthermia. Thirty-six mothers had 44 complications during their pregnancies

Table 3.—Distribution of Infants With SUA* According to Maternal Age and Parity

Pregnancy Status	No. of Infants by Maternal Age, y						
	<20	20-25	26-30	31-35	36-40	>40	Total
Primipara	10	33	22	14	2	0	81
Multipara	0	27	23	21	5	2	78
Total	**10**	**60**	**45**	**35**	**7**	**2**	**159**

*SUA indicates single umbilical artery.

Table 4.—Distribution of Infants With SUA According to Month of Mother's LMP*

Month of LMP	No. (%) of Infants
January	11 (6.9)
February	7 (4.4)
March	12 (7.5)
April	13 (8.2)
May	10 (6.3)
June	20 (12.6)
July	17 (10.7)
August	7 (4.4)
September	17 (10.7)
October	14 (8.8)
November	15 (9.4)
December	16 (10.1)
Total	**159 (100)**

*SUA indicates single umbilical artery; LMP, last menstrual period.

Table 6.—Abnormalities Noted in 26 Placentas

Anomaly	No. of Placentas
Amnion nodosum	8
Infarcts	8
Velamentous insertion of cord	4
Placenta previa	3
True knot in cord	2
Placenta marginata	2
Marginal sinus thrombosis	2
Hydropic changes in chorionic villi	2
Circumvallate placenta	2
Total	**33**

Table 5.—Complications During Pregnancy in 36 Mothers

Complication	No. of Mothers
Antepartum hemorrhage	14
Oligohydramnios	10
Toxemia	9
Hydramnios	6
Urinary tract infection	2
Severe leg cramps	1
Iron deficiency anemia	1
Deep vein thrombosis	1
Total	**44**

Table 7.—Incidence of Associated Congenital Malformations in Infants With SUA*

Malformations	No. (%) of Infants With SUA		
	Died (n=37)	Survived (n=122)	Total (N=159)
Single	2 (5.4)	26 (21.3)	28 (17.6)
Multiple	30 (81.1)	13 (10.7)	43 (27.0)
Total	**32 (86.5)**	**39 (32.0)**	**71 (44.7)†**

*SUA indicates single umbilical artery.
†Percentages do not add to total because of rounding.

(Table 5).

Twenty-six placentas (16.4%) had one or more anomalies (Table 6). A rudimentary second umbilical artery was identified in one of the cords by microscopic examination of the placenta.

One patient had trisomy 21, four had trisomy 18, two had trisomy 13, and one had triploidy. These diagnoses were confirmed by cytogenetic studies in each case.

Seventy-one infants (44.7%) had other congenital malformations in addition to SUA. Associated malformations were more common among infants with SUAs who died (86% vs 32%, Table 7). All the identified congenital malformations by system are listed in Table 8. Screening for renal anomalies with ultrasonography or intravenous pyelography was performed in 27 patients who had no renal symptoms or findings on physical examination and yielded positive results in five patients (18.5%); one infant each had multicystic kidneys, hypoplastic kidneys, horseshoe kidneys, hydronephrosis, and bifid ureter. Six of the 27 infants screened for renal anomalies were high-risk infants in the intensive care nursery, and two (33%) of these infants were found to have renal anomalies. Only three (14.3%) of the 21 infants with SUA in the regular newborn nursery were found to have renal anomalies.

Table 8.—Details of Congenital Malformations Associated With SUA*

Congenital Malformations by System	No. of Infants
Genitourinary	53
Renal agenesis or hypoplasia	8
Renal dysgenesis or dysplasia	8
Hydronephrosis	4
Horseshoe kidney	4
Hydroureter	4
Polycystic kidneys	3
Urachal anomalies	2
Other ureteral anomalies	2
Malrotation of kidney	1
Double ureter	1
Ambiguous external genitalia	6
Hypospadias	4
Persistent cloaca	1
Testicular agenesis	1
Ovarian agenesis	1
Bicornuate uterus	1
Vaginal anomalies	1
Hydrocele	1
Musculoskeletal	59
Talipes (clubfoot)	11
Vertebral anomalies	8
Skull bone and suture defects	6
Clinodactyly or camptodactyly	6
Rib and sternal anomalies	4
Syndactyly	4
Dislocation of hips	4
Amelia and phocomelia	4
Other finger or toe anomalies	3
Rocker-bottom feet	3
Polydactyly	2
Sirenomelia	2
Hyperextensibility of joints	2
Cardiovascular	47
Patent ductus arteriosus	14
Ventricular septal defect	5
Dextrocardia	5
Atrial septal defect	3
Pulmonary stenosis	3
Aortic stenosis	3
Persistent left superior vena cava	3
Truncus arteriosus	2
Bicuspid aortic valve	2
Tetralogy of Fallot	2
Endocardial cushion defect	2
Transposition of great vessels	1
Hemiazygous continuation of inferior vena cava	1
Ectopia cordis	1
Respiratory	15
Pulmonary hypoplasia	13
Choanal atresia	1
Abnormal lobation of lung	1

Table 8.—Details of Congenital Malformations Associated With SUA* (cont)

Congenital Malformations by System	No. of Infants
Gastrointestinal	45
Imperforate anus	10
Tracheoesophageal fistula	6
Omphalocele	6
Meckel's diverticulum	5
Esophageal atresia	4
Agenesis of colon	4
Diaphragmatic hernia	3
Ileovesical fistula	2
Inguinal hernia	2
Gastroschisis	1
Duodenal atresia	1
Malrotation of gut	1
Central nervous	19
Hydrocephaly	5
Cranial nerve anomalies	3
Holoprosencephaly	2
Encephalocele	2
Meningocele	2
Anencephaly	1
Aqueductal stenosis	1
Absent septum lucidum	1
Spina bifida	1
Cerebellar anomalies	1
Special sensory organ	7
Microophthalmia	2
Anophthalmia	2
Cyclopia	2
Proptosis	1
Integumentary	32
Transverse palmar crease	9
Epicanthal folds	8
Webbing of neck	5
Skin tags	5
Hypoplastic nails	2
Hemangioma	1
Widely spaced nipples	1
Absent nipples	1
Miscellaneous	49
Accessory thymus	2
Hypoplastic thymus	2
Accessory spleen	2
Dermoid cyst	1
Cystic hygroma	1
Small atavistic tail	1
Situs inversus	1
Agenesis of spleen	1
Nesidioblastosis of pancreas	1
Agenesis of pancreas	1
Pancreaticosplenic fusion	1
Wide palpebral fissure	1
Hypotelorism	1
Hypertelorism	4
External ear anomalies	11
Micrognathia	9
Cleft lip and palate	8
High-arched palate	1

*SUA indicates single umbilical artery.

COMMENT

The incidence of SUA in reports from departments of obstetrics varies from 0.2% to 1.22%, and, based on autopsies, varies from 2.7% to 12% in departments of pathology.[5] Such discrepancies in the reported incidence of SUA might be due to different methods of examination of the umbilical cords, selected populations, or the proportion of different racial groups. Our finding of 0.28% agrees with that of 0.2% reported by Itoh et al[6] and Lenoski and Medovy.[7] Some authors have found that SUA is more frequent in whites than in blacks and Orientals.[8] Our study shows that in infants of Chinese descent, the incidence of SUA is comparable to that of white infants. Hyrtl[9] noted that SUA occurred predominantly in males, a finding unsubstantiated by subsequent reports.[5,6,8] In our study the incidence in males and females is approximately equal. The predominance of males could reflect the fact that Hyrtl's patient population was based on autopsy material, in which males are usually better represented.

A high incidence of SUA in twins has been observed by Benirschke and Brown.[4] Other studies have not confirmed this observation.[6,8] In our study, 14 infants (8.8%) with SUA were twins. The incidence of twins among infants

with SUA is five times greater than the incidence among controls (1.7%).[10] All twins were discordant for SUA, suggesting that environmental factors may play a more important role than genetic factors in the genesis of this condition. Familial occurrence of SUA has rarely been reported.[11] There were two siblings with SUA in our series.

The reported perinatal mortality rate associated with SUA ranges from 7.6% to 60%, with a mean of 20%.[11,12] In 1964, Fujikura[12] found seven perinatal deaths (18.4%, five stillbirths and two neonatal deaths) among 38 infants with SUA. In 1972, Vlietinck et al[13] found six perinatal deaths (21%, four stillbirths and two neonatal deaths) among 29 infants with SUA. The perinatal mortality rate of 22% in our study concurs with those reported by Fujikura[12] and Vlietinck et al.[13] The high perinatal mortality rate in infants with SUA is a consequence of the associated lethal malformations.

Some authors have noted a high incidence of prematurity and low birth weight among infants with SUA.[4,5] In our study, the mean birth weight of infants with SUA was 2.47 kg, and the mean gestational age was 35.9 weeks. Compared with the controls, SUA occurred in a higher frequency among infants whose birth weights were less than 2.5 kg or who had gestational ages less than 37 weeks (Tables 1 and 2).

There was no difference between infants with SUA and controls in the mode of delivery or Apgar scores.

No consensus has been reached as to whether SUA is related to maternal age, parity, or gravidity.[4,5,8] Our study supports the finding of Saigal and Srivastava[14] that SUA is more common in young primipara and older multipara mothers. Peckham and Yerushalmy[8] observed that more infants with SUA were born to mothers whose LMP was between July and September. Our study supports this association, showing that more infants with SUA were born to mothers whose LMP fell in the months of June, July, September, and December (Table 4). There is no statistical difference in the number of normal newborn infants delivered in any month of the year. Further studies are necessary to determine the cause of this interesting temporal phenomenon.

The incidence of maternal diabetes, epilepsy, toxemia, antepartum hemorrhage, and hydramnios is reported to be higher in infants with SUA.[4,8] In addition to these associations we also observed a high incidence of oligohydramnios (Table 5).

Benirschke and Brown[4] found that 18 (39%) of 46 placentas appeared to have anomalies. These were mostly circumvallation, circummargination, velamentous insertions of the cord, and infarcts. In addition to these anomalies we also found amnion nodosum to be a common finding (Table 6).

An SUA may result from primary agenesis or secondary atrophy of a previously normal umbilical artery. The finding of a rudimentary umbilical artery in one of our patients suggests that, at least in some cases, SUA may result from secondary atrophy of a previously formed umbilical artery.

It has been reported that infants with SUA have a high incidence of autosomal trisomies and other chromosomal abnormalities.[15] In our study, seven infants had autosomal trisomies and one had triploidy, confirming the findings of previous studies.

Among our patients, 44.7% of infants with SUA had other malformations; this incidence is comparable to those in previous reports.[6] There is no known type of malformation or syndrome that is invariably associated with SUA. Even in sireniform and acardiac monsters, both umbilical arteries may occasionally be present.[16] Ballantyne[17] stated that the most common associated malformation was defective development of the bladder together with sirenomelia, while Benirschke and Brown[4] mainly found malformations of the heart and central nervous system. In our series, malformations of the musculoskeletal, cardiovascular, gastrointestinal, and genitourinary systems were frequently encountered. The high incidence of urinary tract abnormalities among infants with SUA was suggested by Feingold et al,[18] who found that eight (33%) of 24 infants had abnormal intravenous pyelograms. This high incidence was not confirmed in subsequent studies.[12,19] In our study, five (18.5%) of 27 asymptomatic infants with SUA had renal anomalies on routine screening with ultrasonography or intravenous pyelography. The incidence was even higher among high-risk infants in the intensive care nursery. Since ultrasonography is a noninvasive procedure, we recommend that renal ultrasonography be done on all infants with SUA.

Infants with SUA deserve to have a thorough physical examination in the neonatal period. The physician should also be alert to the possibility of congenital malformations not evident at the intitial examination.

We thank Murray Feingold, MD, for critically reviewing this manuscript and for his helpful suggestions; Pauline Edge, RN, Kathie Fong, HRT, and Gerry Gabert, RN, of the Health Record Services, Foothills Provincial Hospital, Calgary, Alberta, for data collection; and Kathy Campbell-Brown and Theresa Price for manuscript preparation.

References

1. Vesalius A: *De Humani Corporis Fabrica Libri Septem.*
2. Fallopio G: *Observationes Anatomicae.*
3. Bauhin C: *Theatrum Anatomicum,* vol 1, chap 13, cited by Hyrtl J: *Die Blutgefässe der menschlichen Nachgeburt in normalen und abnormalen Verhälthnissen.* Vienna, Braumüller, 1870.
4. Benirschke K, Brown WH: Vascular anomaly of umbilical cord. *Obstet Gynecol* 1955;6:399-404.
5. Kristoffersen K: The significance of absence of one umbilical artery. *Acta Obstet Gynecol Scand* 1969;48:195-214.
6. Itoh H, Nishimura K, Iwatsubo T: Single umbilical artery: A review of 37 cases. *Acta Obstet Gynecol Jpn* 1976;23:96-100.
7. Lenoski EF, Medovy H: Single umbilical artery: Incidence, clinical significance and relation to autosomal trisomy. *Can Med Assoc J* 1962;87:1229-1231.
8. Peckham CH, Yerushalmy J: Aplasia of one umbilical artery: Incidence by race and certain obstetric factors. *Obstet Gynecol* 1965;26:359-366.
9. Hyrtl J: *Die Blutgefässe der menschlichen Nachgeburt in normalen und abnormalen Verhältnissen.* Vienna, Braumüller, 1870.
10. Heifetz SA: Single umbilical artery: A statistical analysis of 237 autopsy cases and review of the literature. *Perspect Pediatr Pathol* 1984;8:345-378.
11. Adler J, Lewenthal H, Ben-Adereth N: Absence of one umbilical artery and its relationships to congenital malformations. *Harefuah* 1963;65:286-288.
12. Fujikura T: Single umbilical artery and congenital malformations. *Am J Obstet Gynecol* 1964; 88:829-830.
13. Vlietinck RF, Tkhiery M, Orye E, et al: Significance of the single umbilical artery: A clinical, radiological, chromosomal and dermatoglyphic study. *Arch Dis Child* 1972;47:639-642.
14. Saigal S, Srivastava JR: Single umbilical artery: Its incidence and associated congenital malformations. *Indian Pediatr* 1968;5:202-208.
15. Soma H: Single umbilical artery with congenital malformations. *Curr Top Pathol* 1979;66: 159-173.
16. Bryan EM, Kohler HG: The missing umbilical artery: I. Prospective study based on a maternity unit. *Arch Dis Child* 1974;49:844-852.
17. Ballantyne TW: The occurrence of a non-allantoic or vitelline placenta in the human subject. *Trans Edinburgh Obstet Soc* 1898;23:54-80.
18. Feingold M, Fine RN, Ingall D: Intravenous pyelography in infants with single umbilical artery. *N Engl J Med* 1964;270:1178-1180.
19. Harris RJ, VanLeeuwen GV: Single umbilical artery. *J Pediatr* 1968;72:98-99.

Health Status of Children in Self-care

Rickey L. Williams, MD, W. Thomas Boyce, MD

• Are children in self-care more obese, do they miss more school days, and do they make more visits to the school health office than children not in self-care? We undertook a cross-sectional survey of students in ten public elementary schools in Tucson over a two-year period in an attempt to answer these questions. The sample included 503 fifth-grade students, 137 in self-care and 366 not in self-care. Demographic information and data on school absences were obtained from school records. Physical examinations were performed at school. Obesity was assessed using the body mass index calculation, in which body mass index = (body weight in kilograms)/(height in meters)^2. Every visit to the school health office during the 1985-1986 and 1986-1987 school years was recorded for each child. There were no differences in age between those in the self-care and adult-care groups. Boys were more likely to be in self-care, as were non-Hispanic children. There were no differences in weight, body mass index, school days missed, or visits to the school health office between children in self-care and those in adult care. Our findings suggest that, by the criteria used in this study, 11-year-old children in self-care do not suffer more ill health than their counterparts in adult care.

(*AJDC* 1989;143:112-115)

An estimated 8 to 10 million American children younger than 18 years of age are in self-care before or after school. Two to 5 million of these "latch-key" children are grade-schoolers 6 to 13 years of age.[1] Even greater numbers of children are cared for by older siblings.

The effects of self-care on children are unknown. Hypothesized benefits include increased maturity, self-reliance, decision making, freedom, and responsibility.[2] Negative aspects of self-care include feeling or actually being neglected, in danger, isolated, or at medical risk.[1] To our knowledge, no previous study has examined the effects of self-care on children's physical health.

Questions that we attempted to answer are as follows: Are children in self-care more obese? Do children in self-care miss more school days? Do they make more visits to the school health office?

SUBJECTS AND METHODS

Fifth-grade students in ten public elementary schools in Tucson were selected for examination in the present study. These students were selected from a larger two-year project involving kindergarten and fifth-grade students from three different school districts in Arizona enrolled in a project designed to assess unmet health care needs of Arizona schoolchildren. The ten schools were selected for participation in the study based on the geographic and socioeconomic representativeness of each school and the perceived skill, interest, and motivation of the school nurses involved. Informed consent was obtained according to the guidelines of the school district and the University of Arizona Human Subjects Committee.

Several sources of information were available for each student. Age, sex, ethnicity, free or reduced-pay lunch status, and school absence data were obtained from school records. Physical examinations were performed at school by one of two nurse-practitioners. Structured questionnaires were administered to parents and students in English or Spanish. School health office visits were recorded for two years.

Definition of Self-care

Parents completed a standardized questionnaire that asked the following questions: (1) "Where will your child go after school?" (2) "If your child goes home after school, who will be responsible for his or her care?" (3) "Will your child be at home alone in the morning getting ready for school?"

Fifth-grade students were asked the following questions by a research assistant: (1) "What do you usually do after school?" Choices included the following: (*a*) go directly home, (*b*) fool around or play before going home, (*c*) hang around school, (*d*) go to a friend's or neighbor's house, (*e*) go to a day-care center or baby-sitter, and (*f*) other. (2) "What time do you usually get home after school?" (3) "If you went home *right* after school is out, most of the days, would someone be there? If yes, who? If no, what time does an adult usually get home?" (4) "Do you carry a key to the place where you live? If no, is a key to your home left where you can get it if you go home and no one is there?" (5) "Are you ever home alone? If yes, for how long are you usually alone?" Choices included the following: (*a*) 0 to 15 minutes, (*b*) 15 to 30 minutes, (*c*) 30 minutes to one hour, and (*d*) more than one hour. For data analysis purposes, the above categories of time were arbitrarily converted to 7.5, 22.5, 45, and 75 minutes, respectively.

Students were classified as being in self-care under the following conditions: (1) if the students said that they went directly home after school, they "fooled around" or played before going home, or they "hung around school," *and* if they said that nobody or only a sibling was home after school; (2) if the parent said that the child would care for himself or herself after school or that an older brother or sister would be responsible for the child's care; or (3) if the parent said that the child would be home alone in the morning getting ready for school. Students who did not meet at least one of the three criteria were classified as being in adult care.

Physical Examinations

Physical examinations, which included blood pressure, height, and weight measurements as well as a routine physical assessment, were performed on 434 students at school by one of two nurse-practitioners. Height was measured using the height scale on the nurses' scales at school, and weight was measured using a balance-beam scale (height and weight were available for three additional students who did not have a physical examination). These values were converted to metric units, and obesity was assessed using the body mass index calculation, in which body mass index = (body weight in kilograms)/(height in meters).[2-4] A standard-

Accepted for publication Sept 26, 1988.

From the Department of Pediatrics and the Children's Research Center, University of Arizona Health Sciences Center, Tucson (Dr Williams); and the Child Study Unit, Department of Pediatrics, University of California, San Francisco (Dr Boyce).

Reprints not available.

ized checklist was completed for every physical examination. Abnormal physical findings included skin infections, tooth decay, abnormal vision and hearing screenings, and abnormal urine screening results.

Missed School Days

The number of missed school days was obtained from school absence records. Data-entry personnel noted that some families, particularly those with relatives in Mexico, took extended Christmas and Easter breaks; therefore, missed days of school were not necessarily days during which the child was actually ill.

School Health Office Visits

Every visit to the school health office during the 1985-1986 and 1986-1987 school years was recorded on precoded forms and included information on the reason for the visit, the nurse's assessment, and the action taken by the nurse. Each child's total number of visits to the school health office during each of the two years of the study period was summated.

Data Analysis

Student's t test and χ^2 analyses were performed based on the continuous or categorical nature of the data. Analysis of covariance and multiple regression techniques were used to examine and control for the effects of ethnicity and sex.

RESULTS

Of the 503 fifth-graders, 137 (27%) were in self-care before or after school, and 366 (73%) were in adult care. Students frequently changed schools or moved from the district, so a complete data set for every outcome variable is not available for every student. Demographic data are shown in Table 1. There were no differences in age between those in the self-care and adult-care groups. Boys were more likely ($P<.001$) to be in the self-care group, as were non-Hispanic children ($P<.005$).

In response to the question "Are you ever home alone?" 191 (62%) of 308 children in adult care and 100 (82%) of 122 children in self-care answered yes ($P<.001$ by χ^2 analysis). Those who answered yes were asked "For how long are you usually alone?" Children in self-care reported that, when home alone, they were alone for a mean of 45.9 minutes (SD, 30.7 minutes), while children in adult care reported that, when home alone, they were alone for a mean of 25.3 minutes (SD, 28.3 minutes; $P<.001$ by t test). The 22 children classified as being in self-care who stated that they were never home alone were in sibling care after school.

There were no differences ($P>.05$) in height, weight, or body mass index between children in self-care and those in adult care (Table 2). Multiple regression was used to show that these findings held true even though Hispanic children weighed more ($P<.02$) and had a greater body mass index ($P<.02$) than white or black children.

Our body mass index findings of 18.8 ± 3.4 for girls and 18.8 ± 4.0 for boys compare closely with norms from the National Children and Youth Fitness Survey, in which the mean body mass index for 11-year-olds was 19.1 ± 3.6 for girls and 18.7 ± 3.1 for boys (T. R. Lohman, PhD, written communication, March 15, 1988).

Abnormal physical findings were relatively infrequent and were not different between children in self-care and those in adult care. The only abnormali-

Table 1.—Demographic Data on Fifth-Grade Children

Characteristic	All Children	Self-care	Adult Care
Age, y			
Mean (SD)	11.1 (0.6)	11.1 (0.6)	11.1 (0.6)
No. of children	502	137	365
Sex, No. (%)*			
M	224 (45)	80 (58)	144 (39)
F	279 (55)	57 (42)	222 (61)
Ethnicity, No. (%)†			
Native American	12 (2)	7 (5)	5 (1)
Black	26 (5)	8 (6)	18 (5)
Oriental	5 (1)	3 (2)	2 (1)
White	192 (38)	61 (45)	131 (36)
Hispanic	268 (53)	58 (42)	210 (57)

*$P<.001$ by χ^2 test, with 1 df for difference by sex between self-care and adult-care groups.
†$P<.005$ by χ^2 test, with 1 df for difference by ethnic group (Hispanic vs non-Hispanic) between self-care and adult-care groups.

Table 2.—Physical Examination Findings on Fifth-Grade Children

Finding*	All Children (n=453)	Self-care (n=125)	Adult Care (n=328)
Height, cm	142.3 (6.3)	142.4 (6.3)	142.1 (6.3)
Weight, kg	38.3 (9.3)	37.4 (9.4)	38.7 (9.3)
Body mass index	18.8 (3.7)	18.4 (3.6)	19.0 (3.7)

*All values are mean (SD).

Table 3.—School Absence and Health Office Visits for 503 Fifth-Grade Children

Finding*	All Children	Self-care	Adult Care
School days absent			
1985-1986	8.1 (6.6)	7.6 (6.3)	8.3 (6.7)
No. of children	318	80	238
1986-1987	8.2 (7.5)	8.0 (6.5)	8.3 (7.8)
No. of children	391	106	285
School health office visits			
1985-1986	4.7 (9.5)	4.6 (10.9)	4.7 (9.0)
No. of children	331	83	248
1986-1987	5.0 (9.8)	4.6 (9.6)	5.1 (9.9)
No. of children	425	114	311

*All values are mean (SD).

ties that were detected in more than five students were dental caries, abnormal visual acuity, abnormal urinalysis, heart murmur, and abnormal hearing acuity.

There were no differences ($P>.05$) in the number of school days missed between children in self-care and those in adult care (Table 3). Similarly, there were no differences ($P>.05$) in the number of visits to the school health office between children in self-care and those in adult care.

COMMENT

These data fail to demonstrate that children in self-care are more obese, miss more school days, or make more visits to the school health office, even when controlling for gender and ethnicity.

Our definition of self-care makes the assumption that the self-care status of a particular child remains stable over time, which may not necessarily be the case, and is dependent on several factors, such as parental employment and the availability of other types of care. For example, a child who was in self-care from kindergarten until fourth grade and then in fifth grade was no longer in self-care would be classified as not being in self-care, while a child in self-care for the first time during fifth grade would be classified as being in self-care. We did not ask how many months or years the child had been in self-care. However, our data do show that children in self-care were much more likely to have been left home alone, and for longer periods of time, than children in adult care. We used self-reports of self-care status, and some students or parents may not have been willing to admit that children were in self-care. We also did not ask parents if the children were in self-care by choice or because of economic necessity. We included children in the self-care group if an older sibling but no adult was at home, because these children were not in adult care, and older siblings are frequently not much older than the children in question.[1]

Abnormal physical findings were relatively infrequent overall among both children in self-care and those in adult care. These findings agree with those in studies by Yankauer and Lawrence[5,6] more than 30 years ago in which routine detailed physical examinations performed on schoolchildren detected few physical problems.

Recent National Health Examination Survey results suggest that from 1963 to 1980 the prevalence of obesity in American children increased rapidly,[7] and one can postulate that children in self-care are at especially high risk for obesity. We can imagine a scenario in which children in self-care come home, lock the doors, sit down, and watch television while eating snacks instead of running and playing out-of-doors.

In fact, Long and Long[8] studied 53 children in self-care and 32 controls in a black parochial school in Washington, DC, and found that 75% of control children were permitted to play outside after school compared with 57% of children in self-care and 67% of children in sibling care. In the present study, we did not ask whether children were permitted to play outside after school. While it is not clear that such restrictions on activity cause obesity, our data show that children in self-care are not more obese than their counterparts in adult care.

Children in self-care did not miss more school days in our study than did their counterparts in adult care, another indication that there were no differences in perceived health between the two groups. Working parents may find it difficult to stay home from their jobs for each mild communicable illness that their children acquire, and day-care centers frequently exclude children with fever, vomiting, diarrhea, and other communicable diseases.[9] We had expected that children in self-care would be sent to school with minor illnesses and would miss fewer days of school, while children in adult care would be kept home because someone would be there to care for them. On the other hand, some children in self-care may be truant from school. School absence does not necessarily reflect a student's health status but instead may be an indicator of general social maladjustment,[10] and some families of children in self-care may in fact be functioning better than some families in which children are in adult care. The majority of health problems resulting in school absence are due to common, minor, acute infections,[10-12] and excessive absences may result from misperceptions about when to keep a child home from school because of a health problem, excessive parental anxiety, or the vulnerable child syndrome.[12] Demographic and educational characteristics of students may exert a greater effect on absence behavior than health status or receipt of health services.[12]

Children in self-care did not make more visits to the school health office. We had expected that children in self-care would make more visits to the school health office if they were sent to school with a mild illness or that children in self-care would be more likely to visit the school health office for social support that they do not receive if there is nobody at home when they leave school. Also, children in self-care might be expected to make more visits to the school health office for anxiety-related symptoms. As with school absence, school health office visit frequency does not necessarily reflect a student's health status. Students tend to follow the same pattern in health room visit frequency from year to year[13,14]; Lewis and coworkers[14] found that approximately 15% of children accounted for 50% of school health office visits, and the pattern of use was not associated with the presence of known medical problems. Another study found no association between health room visit frequency and abnormal physical examination findings.[13]

In this era of single-parent families and families with two employed parents, many children must return to an empty home after school. In many communities, affordable, conveniently located care programs are unavailable or have long waiting lists; parents in such communities may leave a child in self-care because they have no alternative. In addition, many parents fear that baby-sitters or program personnel may abuse their children; they may feel more comfortable leaving their children home alone than at a center or with a baby-sitter. There will never be enough centers and personnel to permit each of these children to be adequately supervised in programs.

Parents of children in self-care might be made to feel guilty that they are leaving their children in self-care, and arti-

cles in the lay press suggest that being in self-care has negative consequences. For example, results of a recent Lewis Harris and Associates Inc poll were published by the Associated Press and stated that a majority of parents and teachers believe that students would do better in the classroom if adults did not leave the youngsters alone so much after school (*Tucson Citizen*, Sept 3, 1987, p 7A). Our findings suggest that, by the criteria used in this study, 11-year-old children in self-care do not suffer more ill health than their counterparts in adult care.

This study was funded by the Flinn Foundation, Phoenix.

We thank Barbara Sibley, Roxanne Gutman, Roberta Kline, RN, FNP, and the school nurses and health clerks who helped support this project.

References

1. Fosarelli PD: Latchkey children. *J Dev Behav Pediatr* 1984;5:173-177.
2. Garbarino J: Latchkey children: Getting the short end of the stick. *Vital Issues* 1980;30:1-4.
3. Garrow JS, Webster J: Quetelet's index (W/H^2) as a measure of fatness. *Int J Obes* 1985;9:147-153.
4. Keys A, Fidanza F, Karvonen MJ, et al: Indices of relative weight and obesity. *J Chronic Dis* 1972;25:329-343.
5. Yankauer A, Lawrence R: A study of periodic school medical examinations: I. Methodology and initial findings. *Am J Public Health* 1955;45:71-78.
6. Yankauer A, Lawrence R: A study of periodic school medical examinations: II. The annual increment of new 'defects.' *Am J Public Health* 1956;46:1553-1562.
7. Gortmaker SL, Dietz WH Jr, Sobol AM, et al: Increasing pediatric obesity in the United States. *AJDC* 1987;141:535-540.
8. Long T, Long L: *Latchkey Children: The Child's View of Self Care*, ERIC document ED 211229, US Dept of Education, 1981.
9. Shapiro ED: Exclusion of ill children from day-care centers: Policy and practice in New Haven, Connecticut. *Clin Pediatr* 1984;23:689-691.
10. Rogers KD, Reese G: Health studies: Presumably normal high school students: II. Absence from school. *AJDC* 1965;109:9-27.
11. Weitzman M, Klerman LV, Lamb G, et al: School absence: A problem for the pediatrician. *Pediatrics* 1982;69:739-746.
12. Weitzman M, Alpert JJ, Klerman LV, et al: High-risk youth and health: The case of excessive school absence. *Pediatrics* 1986;78:313-322.
13. Rogers KD, Reese G: Health studies: Presumably normal high school students: III. Health room visits. *AJDC* 1965;109:28-42.
14. Lewis CE, Lewis MA, Lorimer A, et al: Child-imtiated care: The use of school nursing services by children in an 'adult-free' system. *Pediatrics* 1977;60:499-507.

Book Review

Paediatric Trauma, by E. K. Alpar and R. Owens, 247 pp, $79.50, Dobbs Ferry, NY, Sheridan House Inc, 1988.

The foreword to *Paediatric Trauma* begins, "All of us have at some time asked ourselves who should treat the injured child. Should it be a paediatrician, a surgeon, an accident physician, or even an 'orthopaedic traumatologist'? Nobody seems to know." However, the book continues ". . . a team led by orthopedic surgeons can." It follows that this text is written from the perspective of pediatric orthopedists in its emphasis on the management of orthopedic, neural, and vascular trauma. Injuries of the head, abdomen, and thorax are covered in 44 pages of the 240-page text.

Several approaches depart from common practice in the United States, many appearing in the chapter entitled "Critical Care." The authors recommend that the child who requires full exposure for examination be covered with a blanket to prevent rapid heat loss (page 47). Although this is acceptable for field care, a radiant warmer is generally preferred for hospital management. The recommendation for initial fluid replacement for the hypovolemic child is 15 mL/kg of "physiological saline" rather than the initial bolus of 20 mL/kg. The use of a flexible wire for assisting in vascular access and the Seldinger technique are not discussed. The use of oxygen and an oropharyngeal airway in the prehospital phase of care is mentioned without reference to indications for endotracheal intubation.

In the chapter entitled "Head Injuries," patients with depressed consciousness are transported in "the semiprone position," a posture which was "de riguer" in the early 1970s, being replaced recently by the rigid supine position with tight immobilization. Again, in a discussion of spinal injuries, "logrolling" is advocated, immobilization is not emphasized, and no mention of iatrogenic injury is made. The neurologic history is used to establish the time course of onset of paralysis; no concern is expressed for recurrence risk in those children with "transient" neurologic disabilities.

In the chapter entitled "Abdominal Injuries," nasogastric tube and urinary catheter placement are described without discussion of precautions in the event of cribriform plate fracture or urethral disruption. Retrograde urethrography is not mentioned.

Although the chapter on hand injuries is much longer than that of thoracic injuries, there are conspicuous omissions, such as failure to mention the phenomenon of regrowth of distal fingertip amputations in children.

In the introduction the editors state: "It has not been our intention to be encyclopaedic . . . but rather to present practical guidance in the management of all aspects of childhood trauma" (page vii). This latter goal has been realized. *Paediatric Trauma* is a readable text with many illustrative diagrams and radiographs. It was compiled by clinicians (representing anesthesiology, radiology, and surgery) who employ a practical approach. However, all aspects of childhood trauma have not been addressed. The text falls short in being neither comprehensive in its coverage of recognition, stabilization, and management nor reliable as a single reference source.

MARTHA BUSHORE, MD
Good Samaritan Hospital
West Palm Beach, FL 33402-3166

Diagnostic Value of Testosterone Therapy in Boys With Delayed Puberty

Paul B. Kaplowitz, MD, PhD

• A brief course of testosterone injections is known to be an effective treatment for boys with constitutional delayed puberty. In this study, data from seven boys at least 14 years old who received testosterone enanthate (100 mg intramuscularly monthly for four months) were analyzed to see if linear and testicular growth responses could be useful diagnostically in excluding growth hormone deficiency (GHD) and isolated gonadotropin deficiency, two conditions that are often difficult to distinguish from constitutional delayed puberty. During four months of testosterone therapy, growth rate increased from 4.0 ± 1.0 cm/y to 10.7 ± 2.3 cm/y, and was greater than 8 cm/y in all patients. Since testosterone-induced stimulation of linear growth is largely GH-mediated, the large increase in growth rate in all boys is considered indicative of GH sufficiency. Testis length, which did not increase during testosterone therapy, increased by 0.6 to 0.8 cm in every patient (from 2.7 ± 0.3 cm to 3.4 ± 0.4 cm) over the following four months, indicating normal gonadotropin secretion and normal pubertal progression; in contrast, the increase in serum testosterone concentrations after discontinuation of testosterone treatment was more variable. It is concluded that the growth response to a four-month course of testosterone is helpful in excluding GHD in boys with delayed puberty, and an additional four months of follow-up is sufficient to document the onset of puberty, thereby eliminating the possibility of isolated gonadotropin deficiency.

(*AJDC* 1989;143:116-120)

Constitutional delayed puberty (CDP), a normal variant growth pattern, is the most common cause of short stature and delayed development in boys older than age 14 years.[1] Although boys with CDP can be allowed to proceed through puberty at their own pace, it is very difficult to predict when virilization and the pubertal growth spurt will begin, since some boys enter puberty as late as age 17 to 18 years. Because many boys with CDP experience considerable anxiety and impaired self-esteem due to their small size and delayed development, it has become an accepted practice to treat such patients with a brief course of testosterone therapy. This therapy has the benefits of both providing a prompt increase in linear growth and genital size and hastening the onset of spontaneous puberty, while not resulting in loss of adult stature due to early epiphyseal closure.

In addition to CDP, the differential diagnosis of delayed puberty includes isolated gonadotropin deficiency (IGD), growth hormone deficiency (GHD) with or without other pituitary deficiencies, and primary gonadal failure. The latter diagnosis is easy to exclude if both testes are palpable and of normal size and serum gonadotropin levels are not elevated. However, both IGD and partial GHD may be very difficult to distinguish hormonally from CDP. In particular, it has been demonstrated that some boys with delayed puberty and short stature will appear GH deficient by standard tests but will have normal GH secretion if tested during spontaneous puberty or after priming with testosterone.[2-4] Furthermore, determination of growth rates in this setting is not as helpful in excluding GHD as in younger children, since it is not uncommon for growth velocity to slow significantly prior to the onset of the pubertal growth spurt.[5] The purpose of this study was to investigate whether the growth response and genital changes observed during and immediately after a four-month course of testosterone therapy in boys with delayed puberty would be helpful diagnostically in excluding both IGD and GHD.

PATIENTS AND METHODS

Records were reviewed for all boys with delayed puberty seen between 1983 and 1987 who met the following criteria: (1) age, 14 years or older; (2) testis length, 3.0 cm or less in longest diameter; (3) serum testosterone level, 1.4 nmol/L or less; and (4) received all four prescribed testosterone injections and returned for all follow-up appointments. Seven boys were identified who met all of these conditions. Pretreatment evaluation included measurements of serum testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), somatomedin C (all performed by Nichols Institute, San Juan Capistrano, Calif), and bone age. In addition, height, weight, stretched penis length, and testicular size (greatest diameter and width) were recorded. All patients were below the fifth percentile in height and weight. Pretreatment growth rate and weight gain velocity (WGV) were calculated from my own measurements obtained at least six months prior to starting testosterone therapy for four patients (patients 1, 3, 4, and 6) and from measurements provided by referring physicians for the other three patients. All patients received testosterone enanthate in oil (100 mg intramuscularly) in four monthly injections. Each child was seen again approximately one month after the fourth injection, and again four months later (approximately eight months after the first injection) to assess growth and genital changes. The only additional laboratory study performed routinely was a serum testosterone measurement five months after the last injection as an indicator of testicular hormone production.

PATIENT REPORT

Patient 1 provides an example of how difficult it is to predict the timing of the onset of pubertal changes in boys with delayed puberty. When first seen at age 15.2 years, his height, which had been in the fifth to tenth percentile between ages 8 and 10 years, was 8 cm below the fifth percentile, and his weight was appropriate for his height. Penis length was 6.8 cm; testis length, 2.6 cm. His

Accepted for publication Sept 19, 1988.

From the Department of Pediatrics, Children's Medical Center, Medical College of Virginia, Richmond.

Reprint requests to Box 140, MCV Station, Richmond, VA 23298 (Dr Kaplowitz).

bone age was three years delayed; testosterone level, 0.6 nmol/L; LH level, 3.1 IU/L; FSH level, 3.7 IU/L; and somatomedin C level, 0.85 U/mL. Four months later, his growth rate was 4.9 cm/y, testis length had increased to 3.0 cm, and penis length was 6.8 cm, but testosterone level was still only 0.8 nmol/L. Since the increase in testicular size indicated that the patient was in early puberty, no treatment was given and the patient was reevaluated in six months (age 16.1 years). At that time, his growth velocity had decreased to 3.7 cm/y, penis and testis length were unchanged, and serum testosterone had increased minimally to 1.0 nmol/L. The patient was then treated with testosterone with prompt increases in linear growth and genital development as described in the "Results" section.

Due to the fact that early testicular enlargement may precede the onset of increased testosterone secretion, virilization, and growth acceleration by many months, it was decided to offer testosterone therapy to boys with testicular size indicative of early puberty (2.6 to 3.0 cm) as well as to those with prepubertal testes (≤2.5 cm), provided that the serum testosterone level was 1.4 nmol/L or less or penis size was clearly prepubertal.

RESULTS

Prior to androgen therapy, growth rate was within the normal prepubertal range for three patients, but less than 4 cm/y in four (Fig 1). After four months of testosterone therapy, there was a marked acceleration in growth rate to 10.7 ± 2.3 cm/y (mean ± SD), with all patients growing at greater than 8 cm/y. Four months later, two patterns were seen. Patients 3 and 5, who had the smallest increase in growth rate, maintained the same growth rate, whereas growth rate declined in the other five patients to between 6 and 8 cm/y, still greater in all cases than their pretreatment growth rates.

The effect of testosterone on WGV was even more dramatic (Table 1). Prior to treatment, the average WGV was 2.6 ± 1.1 kg/y, and there was a fourfold increase to 10.7 ± 2.3 kg/y during testosterone therapy. In three patients (patients 4, 5, and 7), WGV increased to 15 kg/y or more, and the weight gain in only four months was 12% to 15% of their pretreatment weights. Four months later, increased WGV was maintained in the two patients with the smallest increase during testosterone therapy, but decreased to close to pretreatment values or less in the other five.

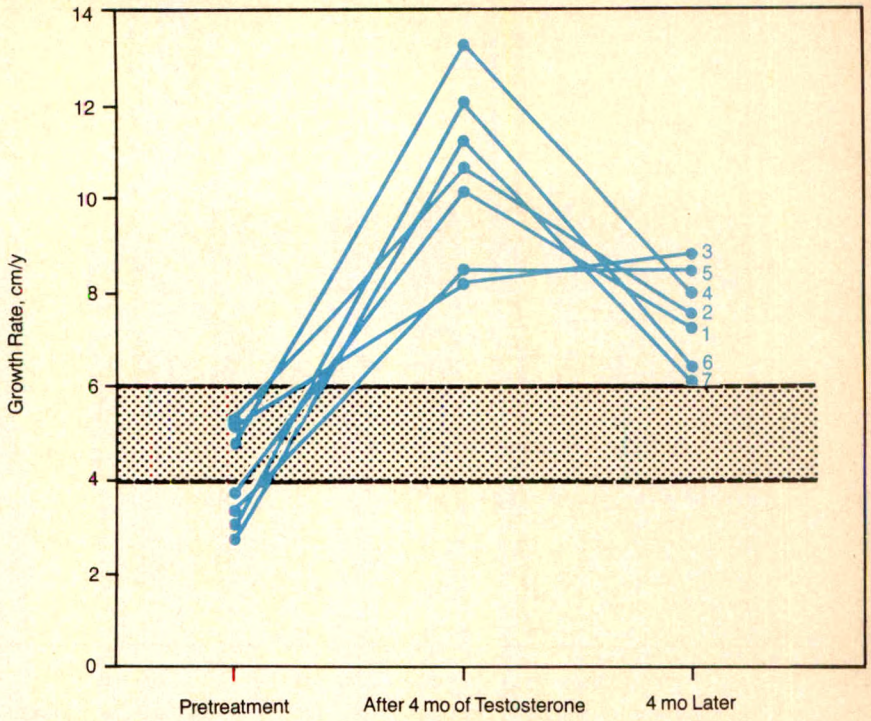


Fig 1.—Effect of testosterone therapy on growth rate in boys with delayed puberty. Patient numbers next to each line correspond to those in Table 2. Shaded area represents tenth to 90th percentile range of growth rate just prior to pubertal growth spurt from Tanner growth rate charts.[5]

Table 1.—Growth and Genital Responses to Testosterone in Seven Boys With Delayed Puberty*

	Age, y	Growth Rate, cm/y	Weight Gain Velocity, kg/y	Penis Length, cm	Testis Length, cm
Pretreatment	15.4 ± 1.0	4.0 ± 1.0	2.6 ± 1.1	6.4 ± 0.5	2.6 ± 0.3
After 4 mo of testosterone	15.7 ± 1.0	10.7 ± 2.3	10.9 ± 3.7	9.3 ± 1.2	2.7 ± 0.3
4 mo later	16.1 ± 1.0	7.5 ± 1.0	3.7 ± 3.1	10.4 ± 1.1	3.4 ± 0.4

*All values are the mean ± SD.

Penis length increased during the four months of intramuscular testosterone therapy from 6.4 ± 0.5 cm to 9.3 ± 1.2 cm (Table 1). During the subsequent four months, there was a continued increase in penis length, but at a much slower rate. Testis length changed little during the four months of testosterone therapy (2.6 ± 0.3 cm before vs 2.7 ± 0.3 cm after). However, during the next four months, testicular length increased to 3.4 ± 0.4 cm, and in all seven patients, this increase was between 0.6 and 0.8 cm (Fig 2). The consistency of this increase in testicular size suggests that following discontinuation of testosterone therapy in boys with CDP, there is a prompt increase in FSH secretion with consequent increase in seminiferous tubule development and, hence, testicular volume.

Table 2 shows the results of endocrine tests performed in the seven boys who received testosterone therapy. Bone age was delayed by 2 to 3½ years in all patients. Pretreatment testosterone concentrations were measured in five of seven and were all 1.4 nmol/L or less. Levels of LH and FSH, measured in four of seven, were variable but were

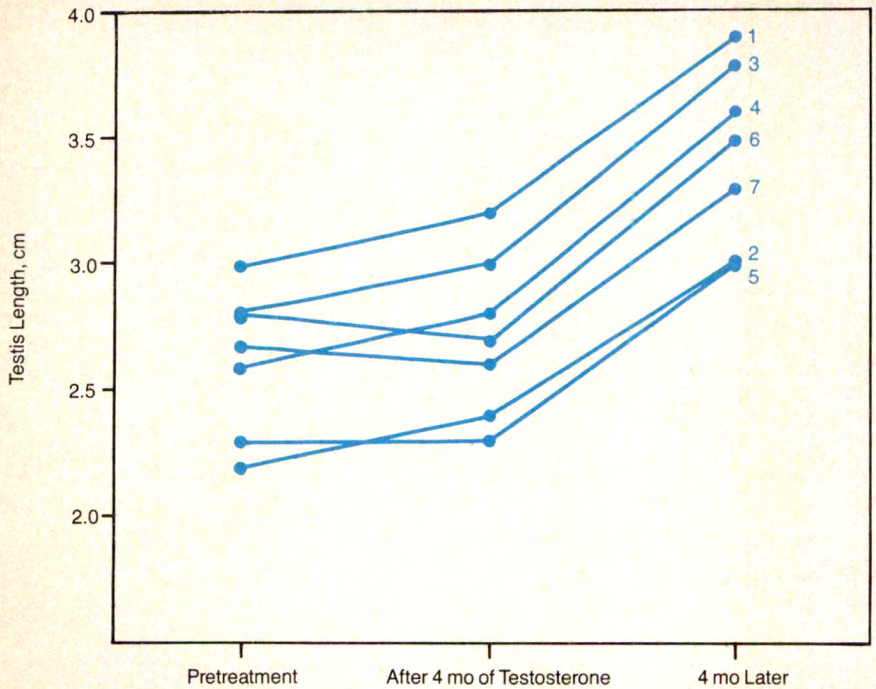


Fig 2.—Effect of testosterone therapy on testicular length in boys with delayed puberty. Patient numbers next to each line correspond to those in Table 2. Prior to treatment, five of seven patients had evidence of early testicular enlargement (length, >2.5 cm) despite low serum testosterone levels.

Table 2.—Endocrine Test Results in Boys With Delayed Puberty*

	Patient No.						
	1	2	3	4	5	6	7
Before therapy							
Age, y	16.1	14.4	14.5	14.2	16.1	15.2	16.9
Bone age delay, y	3	2¼	2¼	2½	2	3	3½
Testosterone, nmol/L	1.0	1.4	ND	ND	0.8	0.5	1.4
Follicle-stimulating hormone, IU/L	3.7	9	ND	ND	<1.6	ND	2.4
Luteinizing hormone, IU/L	3.1	3	ND	ND	2.9	ND	6.6
Somatomedin C, U/mL	0.85	0.8	0.39	1.2	1.0	1.2	0.54
After therapy							
Testosterone, nmol/L	6.1	6.7	ND	0.9	4.1	0.8	4.3

*ND indicates test not done.

not elevated for age in any, which excluded primary hypogonadism. Plasma somatomedin C was determined in all patients to screen for GHD and was in the normal prepubertal range in all but patient 3, in whom it was borderline low (0.39 U/mL). That patient underwent GH testing with clonidine/insulin and had a peak GH level of 20 μg/L. Serum testosterone was determined at the visit occurring approximately five months after the last testosterone injection in six of seven patients. Concentrations were clearly in the pubertal range (4.1 to 6.7 nmol/L) in four of six, whereas in two, the testosterone concentration was still in the prepubertal range. Patient 4, whose testosterone level was only 0.9 nmol/L five months after the last injection, had a level of 3.7 nmol/L six months later, as well as continued growth acceleration (9.5 cm/y) and further testicular enlargement (from 3.6 cm to 3.9 cm). Patient 6, when seen six months later, also had further testicular enlargement (from 3.5 to 3.8 cm), but the increase in his testosterone was slower (from 0.8 to 1.6 nmol/L), and his growth velocity was the same (6 cm/y) as during the four months immediately following testosterone therapy.

COMMENT

The results presented here confirm previous reports that a brief course of testosterone therapy is an effective means of stimulating growth and hastening the onset of puberty in boys with CDP. However, the dosage and duration of testosterone therapy, as well as criteria for patient selection, differed in this study from those of several previous reports. Rosenfeld et al[6] gave four 200-mg injections of testosterone enanthate every three weeks to half of their subjects with delayed puberty, but three of eight of both their treated group and their control group had baseline testosterone concentrations in excess of 3.5 nmol/L, indicating that not all subjects were truly prepubertal. At their follow-up one year later, all treated patients had pubertal concentrations of testosterone and pubertal growth rates (7.2 to 11.6 cm/y), whereas two of eight untreated patients still had prepubertal testosterone concentrations and four of eight were still growing at less than 6 cm/y. Thus, while many boys with delayed puberty will enter puberty spontaneously during a one-year period of observation, this clearly cannot be insured. A more recent report from the same center indicated that height in 11 treated patients whose growth was complete did not differ significantly from their pretreatment predicted adult height.[7] Martin et al[8] compared the effects of three doses of testosterone enanthate (200 mg, 100 mg, and 50 mg) given monthly for nine to 12 months to boys at least 14 years old with testicular length of less than 3.2 cm.[8] All groups had significant growth acceleration to 10 to 12 cm/y during therapy but the 200-mg group had the largest deceleration (to 4.6 cm/y) during the year following therapy, and their adult heights averaged 3.3 cm less than pretreatment predicted height ($P<.01$). Adult height in the 50-mg and 100-mg groups was not significantly different from predicted adult height. Donaldson and Savage[9] recently reported that in 36 boys with a mean age of 14.8 years treated with 125

mg of testosterone enanthate monthly for three months, growth rate increased from 4.4 to 9.8 cm/y at six months, and no loss in predicted adult height was observed at between 0.5 and two years after the start of treatment. These reports indicate that although prolonged treatment with higher doses of testosterone may result in some loss of adult height in boys with delayed puberty, lower doses (50 to 125 mg) or higher doses given for short periods have no discernible effect on adult height.

Previous studies of testosterone treatment for delayed puberty have not emphasized the usefulness of this treatment in excluding the diagnosis of GHD. It has been observed that there is a dip in the growth rate curve just prior to the pubertal growth spurt,[5] and in this report, four of seven subjects had pretreatment growth rates below 4 cm/y. Although it is a common practice to investigate GH secretion in children growing at less than 4 cm/y, such studies are of limited value in diagnosing true GHD in boys with delayed puberty, since these patients often have subnormal GH secretion that normalizes following spontaneous puberty or androgen priming.[2-4] Link et al[10] have demonstrated that increased growth velocity in five prepubertal boys receiving testosterone correlated with a significant increase in mean 24-hour GH concentrations (from 2.3 ± 1.8 μg/L to 6.4 ± 2.4 μg/L) as well as increased plasma somatomedin C concentrations (0.82 ± 0.46 U/mL to 2.3 ± 0.4 U/mL). Thus, it can be argued that a substantial increase in growth velocity during testosterone treatment is by itself a valid measure of GH sufficiency. On the other hand, testosterone given to GH-deficient subjects fails to elicit its normal growth-promoting effect.[11,12] For example, boys with anorchism or IGD given testosterone replacement at a pubertal bone age had increases in mean growth rate from 5.8 to 11.0 cm/y and 4.4 to 10.2 cm/y, respectively, during the first six months, whereas in boys with combined GHD and gonadotropin deficiency, growth rate increased only from 3.8 to 4.5 cm/y after six months of testosterone therapy.[12] Furthermore, whereas seven boys with precocious puberty and normal GH secretion by provocative testing all had growth rates of 8 to 14 cm/y, five boys with pubertal steroid levels and GHD had growth rates of only 4.0 to 6.3 cm/y.[13] In the present study, growth rate during four months of testosterone treatment was 8.3 to 13.4 cm/y, consistently greater than observed in the GH-deficient pubertal children. It should be noted that part of the growth-stimulatory effect of sex steroids may be independent of increased GH secretion, since in GH-deficient children receiving constant GH replacement, administration of the anabolic steroid fluoxymesterone resulted in a greater rate of growth than that observed with GH alone.[14] Although this study did not include a group of GH-deficient testosterone-treated subjects for comparison, it is reasonable to conclude from previous reports that increases in growth rate to greater than 8 cm/y during testosterone therapy are unlikely to be observed in children with true GHD and are therefore indicative of GH sufficiency. Therefore, GH testing (with or without androgen priming) might be necessary only for those boys with delayed puberty and subnormal growth rate who fail to have a substantial increase in growth rate during four months of testosterone therapy.

The problems of hormonally distinguishing CDP from IGD are well known, since there is considerable overlap between the two conditions in their serum androgen levels and basal and gonadotropin-releasing hormone–stimulated gonadotropin levels.[1,15] Although micropenis, anosmia (Kallmann's syndrome), and/or normal stature may suggest that a boy with delayed puberty has IGD rather than CDP, the diagnosis may not be secure in some patients unless puberty fails to occur by age 18 to 19 years. The data presented here suggest that the testicular response to a four-month course of testosterone therapy may exclude the diagnosis of IGD without the need for prolonged waiting and uncertainty. During the treatment, as expected, testicular size did not change, since exogenous androgens in peripubertal boys suppress gonadotropin secretion. However, four months later, there was striking and uniform increase of 0.6 to 0.8 cm in testis length. When this increase was expressed in terms of testicular volume (calculated from the formula $\pi/6 \times \text{length} \times \text{weight}^2$), the mean increase was from 4.2 ± 1.5 mL to 6.9 ± 1.6 mL, or an average of 2.7 mL in four months. Since during normal puberty, the most rapid rate of testicular growth (observed during the year prior to peak height velocity) is 4.9 mL/y,[16] it is possible that testosterone treatment primes the hypothalamic-pituitary-gonadal axis for a more rapid increase in FSH secretion (or a brisker testicular response to FSH) than would normally occur. The conclusion that rapid testicular growth after testosterone therapy reflects normal gonadotropin function would have been strengthened by demonstrating that a four-month course of testosterone in teenage boys with IGD did not result in subsequent testicular enlargement. During the period of this study, only one adolescent boy with IGD (Kallmann's syndrome) was seen at this institution; his testes remained infantile at age 17 years after three courses of testosterone (six months or longer). Furthermore, a recent report of 20 boys with IGD, most of whom were 15 to 20 years old and had received testosterone for virilization, stated that 75% had small prepubertal testes (<2 mL) and none had a testicular volume greater than 4 mL.[17]

It is of interest that the serum testosterone level measured five months after the last testosterone injection confirmed the onset of puberty in only four of the six patients in which it was determined. However, in the two patients in whom testosterone level was still 1.4 nmol/L or less, a visit six months later showed definite pubertal progression and increasing testosterone concentrations. This lag between increased testicular size and increased testosterone production in these two patients could reflect a greater increase in FSH than in LH secretion after stopping testosterone therapy. It should be noted, however, that in early puberty, pulsatile LH secretion and testosterone production initially increases nocturnally prior to its increase during the day,[18] and the two patients in question may have had pubertal testosterone concentrations at night even though their daytime concentrations remained low. These findings suggest that the rate at which testosterone secretion increases following four months of testosterone injections

may be quite variable, and that increasing testicular size is a more reliable indicator of the onset of spontaneous puberty than is a single daytime testosterone determination.

Based on the results presented here, four monthly 100-mg injections of testosterone enanthate can be considered an effective, simple, and inexpensive treatment for CDP. During the four-month treatment period, there was acceleration of linear growth as well as a marked increase in weight gain and genital size, which are reassuring for boys with CDP who are usually anxious about how they compare with their larger and more developed peers. Although more frequent erections were noted, this was not felt to be excessive in any patient. At the follow-up visit four months later, growth rate slowed in most boys (presumably because it takes time for endogenous testosterone production to increase to the level provided by the testosterone injections), but was still above the normal prepubertal range, and the finding of testicular enlargement allowed patients to be reassured that puberty was progressing normally. It is possible that lower doses of testosterone or fewer injections could achieve the same positive results, but there is apparently no need in most cases to use either more than 100 mg per injection or more than four injections. Short courses of the oral anabolic steroids fluoxymesterone and oxandrolone have also been shown to be safe and effective in stimulating linear growth in boys with delayed puberty,[19,20] but there are no controlled studies that compare these agents with testosterone. Although GH therapy may increase growth rate in short non–GH-deficient boys, many of whom presumably have constitutional growth delay,[21,22] its short-term effect is generally not as dramatic as that observed with testosterone. Due to its expense, it should probably not be widely used in boys with CDP unless studies currently in progress demonstrate a clear advantage over a short course of testosterone therapy in terms of final adult stature.

Prior to starting testosterone treatment, it is important to exclude chronic disease as a cause of delayed puberty by history and physical examination. It is helpful to measure bone age, which should be at least two years delayed, and serum testosterone to confirm prepubertal status, since patients with testosterone concentrations of 3.5 nmol/L or greater appear to progress through puberty normally in the next 12 months without any therapy.[6] The LH and FSH determinations are of little value in excluding IGD but will aid in excluding primary hypogonadism; however, they may be unnecessary in patients with early testicular enlargement (length, 2.6 to 3.0 cm). Plasma somatomedin C measurement may help to identify the child with severe GHD, but if the result is normal, and there are no signs or symptoms of an intracranial lesion such as a craniopharyngioma, GH testing and radiologic investigations could be deferred even in children with growth rates as low as 3 to 4 cm/y. These results indicate that simple height and testicular measurements done at four and eight months after starting testosterone therapy will exclude GHD and IGD and confirm the diagnosis of CDP in most boys with delayed puberty. More detailed endocrine and radiologic evaluations and consideration of GH therapy might therefore be reserved for the occasional patient who does not have the responses to testosterone treatment that are characteristic of boys with CDP.

References

1. Styne DM: Delayed puberty, in Hintz RL, Rosenfeld RG (eds): *Growth Abnormalities*. New York, Churchill Livingstone Inc, 1987, pp 141-165.
2. Martin LG, Clark JW, Connor TB: Growth hormone secretion enhanced by androgens. *J Clin Endocrinol Metab* 1968;28:425-428.
3. Penny R, Blizzard RM: The possible influence of puberty on the release of growth hormone in three males with apparent isolated growth hormone deficiency. *J Clin Endocrinol Metab* 1972;34:82-84.
4. Gourmelen M, Pham-Hau-Trung MT, Girard F: Transient partial hGH deficiency in prepubertal children with delay of growth. *Pediatr Res* 1979;13:221-224.
5. Tanner M, Whitehouse RH, Takaishi M: Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1965. *Arch Dis Child* 1966;41:454-471.
6. Rosenfeld RG, Northcraft BA, Hintz RL: A prospective, randomized study of testosterone treatment of constitutional delay of growth and development in male adolescents. *Pediatrics* 1982;69:681-687.
7. Wilson DM, Kei J, Hintz RL, et al: Effects of testosterone therapy for pubertal delay. *AJDC* 1988;142:96-99.
8. Martin MM, Martin ALA, Mossman KL: Testosterone treatment of constitutional delay in growth and development: Effect of dose on predicted versus definitive height. *Acta Endocrinol* 1986;suppl 279:147-152.
9. Donaldson MDC, Savage DCL: Testosterone therapy in boys with delayed puberty, abstracted. *Pediatr Res* 1988;23:125A.
10. Link K, Blizzard RM, Evans WS, et al: The effect of androgens on the pulsatile release and the twenty-four-hour mean concentration of growth hormone in peripubertal males. *J Clin Endocrinol Metab* 1986;62:159-164.
11. Zachmann M, Prader A: Anabolic and androgenic effect of testosterone in sexually immature boys and its dependency on growth hormone. *J Clin Endocrinol Metab* 1970;30:85-95.
12. Aynsley-Green A, Zachmann M, Prader A: Interrelation of the therapeutic effects of growth hormone and testosterone on growth in hypopituitarism. *J Pediatr* 1976;89:992-999.
13. Rappaport R, Prevot C, Brauner R: Somatomedin-C and growth in children with precocious puberty: A study of the effect of the level of growth hormone secretion. *J Clin Endocrinol Metab* 1987;65:1112-1117.
14. MacGillivray MH, Kolotkin M, Munschauer RW: Enhanced linear growth responses in hypopituitary dwarfs treated with growth hormone plus androgens versus growth hormone alone. *Pediatr Res* 1974;8:103-108.
15. Dunkel L, Perheentupa J, Virtanen M, et al: Gonadotropin-releasing hormone test and human chorionic gonadotropin test in the diagnosis of gonadotropin deficiency in prepubertal boys. *J Pediatr* 1985;107:388-392.
16. Zachmann M, Prader A, Kind HP, et al: Testicular volume during adolescence: Cross-sectional and longitudinal studies. *Helv Paediatr Acta* 1974;29:61-72.
17. Van Dop C, Burstein S, Conte F, et al: Isolated gonadotropin deficiency in boys: Clinical characteristics and growth. *J Pediatr* 1987;111:684-692.
18. Boyar RM, Rosenfeld RS, Kapen S, et al: Human puberty: Simultaneous augmented secretion of luteinizing hormone and testosterone during sleep. *J Clin Invest* 1974;54:609-618.
19. Stanhope R, Bommen M, Brook CGD: Constitutional delay of growth and puberty in boys: The effect of a short course of treatment with fluoxymesterone. *Acta Paediatr Scand* 1985;74:390-393.
20. Stanhope R, Buchanan CR, Fenn CG, et al: Double-blind placebo controlled trial of low dose oxandrolone in the treatment of boys with constitutional delay of growth and puberty. *Arch Dis Child* 1988;63:501-505.
21. Gertner JM, Genel M, Gianfredi SP, et al: Prospective clinical trial of human growth hormone in short children without growth hormone deficiency. *J Pediatr* 1984;104:172-176.
22. Costin G, Kaufman FR: Growth hormone secretory patterns in children with short stature. *J Pediatr* 1987;110:362-368.

Reprint Requests

How and Why They Were Made

Alexander K. C. Leung, MBBS, FRCPC, FAAP, MRCP(UK), MRCPI

• Of the 457 reprint requests that I received over a two-year period, 432 (94.5%) came in the form of preprinted postcards and the remainder came in the form of letters. Only 235 (51.4%) were signed. There were 450 (98.5%) requests for one copy of the article and seven (1.5%) requests for more than one copy. Three hundred ninety-five (86.4%) requests were for one article, and 62 (13.6%) requests were also for any other previous articles on the subject. None of the reprint requests arrived with a self-addressed stamped envelope. One hundred twenty-seven (27.8%) requests came with a return address stick-on label. Most reprint requests were in English and came from the United States and countries in eastern Europe. A questionnaire was sent to each of the 457 persons who requested a reprint to determine how and why the request was made. There were 259 (56.7%) replies available for analysis. One hundred ninety-three (74.5%) reprint requests were made by the individuals requesting the reprint and 59 (22.8%) were made by their secretaries. The majority (81.1%) learned about the article and address from *Current Contents*. Forty-four (17%) had read the article (or abstract) before the reprint request was made. The two most common reasons given for the request were the unavailability of the journal and the high quality of the reprint. Two hundred fifty-six (98.8%) of the persons requesting reprints found them very useful.

(*AJDC* 1989;143:121-123)

The cost and amenities of reprint requests have often been a topic of discussion and editorial comment. The exact origin of reprint requests is obscure, but the practice was already widespread by the early 1920s.[1] Despite the widespread availability of photocopying facilities, requesting reprints of articles from medical journals is still a time-honored means of obtaining medical information. The motives and the ways of obtaining reprints may vary with the individual requesting a reprint. I conducted a prospective study to find out how and why reprint requests were made.

Accepted for publication Sept 19, 1988.

From the Department of Pediatrics, University of Calgary, Alberta Children's Hospital, Canada.

Reprint requests to Alberta Children's Hospital, 1820 Richmond Rd SW, Calgary, Alberta, Canada T2T 5C7 (Dr Leung).

METHODS

From January 1986 to December 1987, I received 474 reprint requests for my 14 articles published in various medical journals. Seventeen requests were not included in the study: 12 were for reprints of articles not written by me, four were duplicate requests, and one request was illegible.

Of the remaining 457 reprint requests, 390 were from physicians, 13 from dentists, 41 from doctors of philosophy, two from veterinarians, six from librarians, four from drug information services, and one from a pharmaceutical company.

A questionnaire, as shown in Table 1, was sent to each individual who requested a reprint. No response is defined as no response received by four months from the date of mailing. The information on all reprint requests as well as on the returned questionnaires was collated and analyzed.

RESULTS

Four hundred thirty-two (94.5%) reprint requests came in the form of preprinted postcards, while the remaining 25 (5.5%) were in the form of letters. Of the 457 reprint requests, 235 (51.4%) were signed. Four hundred fifty (98.5%) requests were for only one copy of the article while the remaining seven (1.5%) requests were for more than one copy. Three hundred ninety-five (86.4%) individuals requested only one article, and 62 (13.6%) requested, in addition, "any other previous papers related to the same subject."

None of the reprint requests arrived with a self-addressed stamped envelope. One hundred twenty-seven (27.8%) requests came with a return address stick-on label. Five (1.1%) requests specified to "please return this card if reprints are not available."

Two hundred ninety-four (64.3%) requests were in English only, 161 (35.2%) requests were in English and one or more other languages, and two (0.4%) requests were in other languages.

There were 259 (56.7%) responses to the questionnaires. The countries of origin of these requests are shown in Table 2. Analysis of the returned questionnaires showed that 193 (74.5%) of the requests were made by the requesting individuals, 59 (22.8%) by their secretaries, four (1.5%) by their associates, two (0.8%) by medical students, and one (0.4%) by a husband who was also a physician.

Two hundred ten (81.1%) individuals who requested reprints learned about my article from *Current Contents*, three (1.2%) from *Science Citation Index*, two (0.8%) from *Index Medicus*, 28 (10.8%) from the appropriate journal, nine (3.5%) from Automatic Subject Citation Alert-Institute for Scientific Informational and Technological Information (Israel), and one (0.4%) each from National Institute on Drug Abuse, Canada Institute for Scientific Information, National Clearinghouse for Alcohol Information, and *Deutsche Medizinishe Wochenschrift*. All of the individuals who requested reprints obtained my address from the same source from which they learned about my article, with the exception of the two requesters who learned about my article from *Index Medicus* and then obtained my address from the appropriate journals.

Forty-four (17%) individuals had read

Table 1.—Questionnaire Sent Out to the Reprint Requesters

A. Who made the reprint request?
   Yourself _____
   Your secretary _____
   Other (please specify) _____
B. Where did you (a) learn about my article? (b) get my address?
   Current Contents _____ _____
   Science Citation Index _____ _____
   Index Medicus _____ _____
   The appropriate journal _____ _____
   Other source (please specify) _____ _____
C. Had you read my article or the abstract before the reprint request was made?
   Yes _____ No _____
D. Please indicate the most important reason for the reprint request (choose one answer only)
   1. The journal was not available locally _____
   2. Photocopying facilities were not available locally _____
   3. Photocopying was prohibited by copyright regulations _____
   4. High quality of the reprint _____
   5. Your local institution would pay for the mailing of the reprint cards or letters but not for the photocopying _____
   6. Others (please specify) _____
E. Do you find reprints useful?
   Yes _____ No _____

Table 3.—Reasons Given by the Reprint Requesters for the Reprints

Reason for the Reprint	No. of Responses
Journal not available locally	156
Photocopying facilities not available locally	8
Photocopying prohibited by copyright regulations	7
High quality of the reprint	95
Local institution would pay for the mailing of the reprint cards (letters) but not for the photocopying	14
Library not readily accessible	8
Photocopying time-consuming	8
Personal contact with the author	1
Space-saving for reprint libraries	8

Table 2.—Countries of Origin of Reprint Requests

Countries	Total No. of Requests	No. With Returned Questionnaire
Argentina	6	2
Australia	3	1
Austria	4	2
Bangladesh	2	0
Belgium	2	1
Brazil	1	0
Bulgaria	1	0
Canada	29	22
Colombia	2	0
Cuba	10	2
Czechoslovakia	34	16
Ecuador	1	0
Finland	1	1
France	18	15
Germany		
East	50	24
West	25	10
Hungary	9	5
Iceland	1	0
India	1	0
Israel	24	16
Italy	8	6
Japan	3	1
Malta	1	1
Mexico	4	2
Netherlands	8	3
Nigeria	1	1
Norway	4	3
Paraguay	1	0
Poland	17	10
Romania	5	1
Soviet Union	6	3
Spain	9	6
Switzerland	6	2
Turkey	1	1
United Kingdom	1	0
United States	156	101
Venezuela	1	0
Yugoslavia	1	1

my article (or abstract) before the request was made. One (0.4%) individual did not answer this question. The remaining 214 (82.6%) confirmed that they had not read the article (or abstract) before the request was made.

Although the respondents were asked to choose only one response to the question, "Please indicate the most important reason for the reprint request," 38 gave more than one answer. The reasons for the reprints are summarized in Table 3.

Two hundred fifty-six (98.8%) individuals found the reprints very useful while one (0.4%) indicated that the article had not yet been read. Two (0.8%) did not answer this question. Twelve individuals remarked that, in their countries, obtaining reprints is the only way of having access to recent achievements in medicine. One reprint requester remarked that he "does hope that editors will not influence others to discontinue the sending or requesting of reprints." Three respondents asked me to send them the results of my study when it is published.

COMMENT

Reprint requests, which began as a matter of courtesy among a small group of scholars in the past, are common today despite the availability of photocopying. Custom dictates that authors provide reprints at no cost to the recipients. Reprint requests using preprinted postcards are easy to use but can be abused. Some authors send reprints only to those who write personally to explain their interest.[2,3] Others argue that most scientific investigators who have a real need for a specific reprint do not have the time to write or dictate letters detailing why they desire it.[4] The requests, however, should be signed. In the present study, only 235 (51.4%) reprint requests were signed.

Reprints are costly to authors. Some requests are for reprints of every article published, often requesting two to five copies, for assembly of libraries at low cost. The author incurs the financial burden and this courtesy should not be abused. In this study, seven (1.5%) individuals requested more than one copy of the article. It may not be unreasonable to request previous articles on a related

subject provided the individual is sincerely interested in the subject. In my study, 62 (13.6%) individuals made this request.

From time to time, letters to editors contain complaints from authors about the expense involved in meeting reprint requests. It has been suggested that reprint requesters should enclose a self-addressed, stamped envelope to share the costs in a more equitable manner. A practical problem is that some individuals may not know what size envelope they should enclose and the exact amount of postage they should affix to the envelope. This is especially so for international mailings in which return postage cannot be provided. In the present study, none of the reprint requests came with either a self-addressed envelope or return postage, but 27.8% did come with a return address stick-on label.

Requesting reprints may go unrewarded. Hamilton-Miller[5] kept a record of his requests over a five-year period and found that the return rate ranged from 72.7% to 78.1%. Therefore, it is advisable to keep a record of requests and to ask the author to return the card (or letter) if reprints are not available. Only 1.1% of requests in the present study requested notification if reprints were not available.

My study confirms the finding[6-8] that most reprint requests are in English and come from the United States and countries in eastern Europe.

There is a general impression that most individuals who make requests have never seen the requested article. At best they have seen the title in a periodical like *Current Contents*. For some individuals the duty of scanning lists of titles or key words may have been delegated to a secretary. Of the 482 requests received by Posen and Posen,[7] only 240 (49.8%) had the correct address as shown in their article; 192 (39.8%) bore an address identical in every respect with that given in *Current Contents*; and the remaining 50 (10.4%) used an intermediate form of address. Clark[9] reported that two thirds of the request cards bore a particular error in her mailing address and it was the identical error that appeared with the citation of her article in the Institute for Scientific Information list. She inferred that two thirds of the requests for reprints came from individuals who had not read her article but had seen the title listed by an information service. Pickles[10] had a letter published in *Nature* under a deliberately misleading title "Prostaglandins: An experiment." In the letter, Pickles gave his previous experience as a victim in the reprint game and made it quite clear that one object of his letter was to fool some of the culprits. Although the letter specifically asked the reader not to send for a reprint, more than 100 reprint cards were received. In April 1967, the *British Medical Journal* reprinted Lister's original article of 1867.[11] Reprint requests were subsequently sent to Dr Joseph Lister, University of Glasgow, Scotland. In the present study, although 74.5% of individuals made the request themselves, only 17% had read my article (or abstract) before they made the requests. The majority (81.1%) learned about my article from *Current Contents*.

The motivation for reprint requests varies. People from some countries may request reprints because journals are not available. From Zambia, a medical superintendent of a 380-bed hospital wrote that he had three photocopiers (courtesy of the United Nations Children's Fund) but that they required special paper, developer, etc, that was unavailable.[12] In any case, his hospital received no journals to photocopy. In the United States, restrictions on photocopying may be an important factor. Publishers of journals financed largely by subscriptions regard nonenforcement of copyright regulations as a threat to the existence of such journals. The making of a photocopy of a published article for personal use, however, does not infringe on present copyright laws.[13] However, copyright laws in Canada are presently under review. Some journals do not participate in the Copyright Licensing Agency or in the US Copyright Clearance Center and hold the view that single copies for research or study can be made without permission or payment.[14]

Photocopying produces typeface and diagrams quickly and cheaply, but photographs or photomicrographs are poorly reproduced. Thus, reprints are essential when photographs are fundamental to the understanding of an article. Some request reprints because a library is not readily accessible. Others request reprints because they would like to have a personal contact with the author.[2] Buisseret[3] cited an instance where an individual asked for reprints from foreign authors because his daughter was a keen stamp collector. The two most popular reasons for reprint requests were the unavailability of the journal and the high quality of the reprint.

The author thanks Lane Robson, MD, FRCPC, for help in designing the questionnaire and Kathy Campbell-Brown for expert secretarial assistance.

References

1 . Lewis RK: Responses to reprint requests. *J Med Educ* 1972;47:827-829.
2. Prowse GA: Reprints abroad. *Science* 1965; 148:313-314.
3. Buisseret PD: More on reprints. *N Engl J Med* 1981;304:1609-1610.
4. Pickwell GV, Douglas E: Reprint system debated. *Science* 1965;147:677-678.
5. Hamilton-Miller JMT: The reprint game. *Br Med J* 1977;1:509.
6. Woodruff M: Reprints or authorised photocopies? *Lancet* 1987;1:451.
7. Posen S, Posen JS: The geography of reprint requests. *J Med Educ* 1969;44:648-654.
8. Briggs MH, Briggs M: Hormones and blood chemistry. *Nature* 1972;240:490-491.
9. Clark ME: Reprint unlimited. *Science* 1967; 155:776-777.
10. Pickles VR: The reprint game. *Br Med J* 1977;1:509-510.
11. Fleming CM: Intimations of immortality? *Br Med J* 1967;3:53.
12. Macfarlane J, Cullen MH, Banks DC: Why request reprints? *Br Med J* 1981;283:1614.
13. Wright C: *Libraries and Copyright: A Summary of the Arguments for Library Photocopying*. Chicago, The American Library Association, 1976, pp 41-44.
14. Copyright restrictions, editorial. *Lancet* 1984;2:1476.

Advertisement

A NEW LOOK AT FORMULA ALLERGY AND INTOLERANCE: IS SOY EFFECTIVE?

Intestinal closure as an immunologic defense

As one of their many adaptations to the extrauterine environment, formula-fed neonates must also develop the ability to digest and absorb nutrition from ingested infant formula. This is no small task; it includes having to develop physiologic and immunologic defenses against the absorption of any of the more than 25 distinct, potentially allergenic proteins of cow's milk (notably beta-lactoglobulin, alpha-lactalbumin, and bovine serum albumin) or any of the four macromolecular soy proteins (notably glycinin). This maturational process is known as *intestinal closure.*

Breast milk is nutritionally and immunologically ideal, and, except for the occasional presence of intact allergens from the maternal diet, causes no problems for the immature intestinal mucosa. If, however, the infant ingests cow's milk- or soy-based formulas before intestinal closure can occur, the large intact proteins can flatten the villi[1,2] and/or cause them to atrophy, increasing the permeability of the lumen and rendering it more vulnerable to penetration by proteins that could provoke systemic or local hypersensitivity reactions, including eczema, asthma, diarrhea, and colic. In addition, episodes of gastroenteritis can damage mucosal surfaces, compromising the effectiveness of the barriers and leading to massive penetration by the allergens.[3] This increases the likelihood of further allergic manifestations.[4]

Early history good for soy protein . . .

Hill and Stuart[5] first proposed soybean preparations as a substitute for cow's milk in infant formulas in 1929. No allergic reactions to soy were recorded at the time, perhaps due to limited clinical experience, or perhaps because soy allergy may take weeks to develop, making soy-based formulas appear nonallergenic at the outset. In 1960 a series of case reports appeared citing gastrointestinal and "allergic" reactions to soy protein, followed by additional reports of soy protein intolerance concomitant with cow's milk protein intolerance, and positive intracutaneous tests of soybean protein in allergic children who received soy protein formula in infancy.[6]

. . . But soy may be as antigenic as cow's milk

Evidence is accumulating that sensitivity to soy is more widespread than was once believed, with estimates averaging around one fourth of infants who are sensitive to cow's milk,[7,8] but reaching as high as 40% of these infants.[9] Lothe et al[10] noted that 53% of colicky infants showed adverse reactions to soy protein formula. May et al[11] found that the feeding of soy protein formula from birth to 112 days did not lessen the antibody response to cow's milk protein products fed subsequently. A study by Eastham et al[4] also suggests that soy protein may be as antigenic as cow's milk protein. Thus there is evidence that soy protein formula may neither prevent the development of allergies nor resolve symptoms of cow's milk intolerance in many infants, and has been shown to prolong or aggravate these symptoms in some infants. For these reasons the American Academy of Pediatrics Committee on Nutrition (AAP/CON) recommends *against* the use of soy protein formulas in the dietary management of documented clinical allergic reaction to cow's milk protein, or in the routine management of colic. Instead, AAP/CON recommends protein hydrolysate formulas in these cases.[6]

Alternatives

Casein hydrolysate formula is hypoallergenic, but its expense (more than twice the price of routine formulas) prohibits routine use. Many parents also report that casein hydrolysate formulas smell and taste unpleasant.

A recently developed whey hydrolysate formula, however, may provide an economical alternative to soy for the management of colic or formula intolerance. As a routine formula, it can delay and may even prevent the development of allergy symptoms in infants at high risk due to a family history of atopy. This hydrolyzed whey protein formula is truly hypoallergenic, moderately priced for long-term or routine use, and has a pleasant taste and aroma. For a monograph on the new product, GOOD START H.A.™ Iron Fortified Hypoallergenic Infant Formula, write to Carnation Nutritional Products, ACS, 4144 Howard Ave, Kensington, MD 20895.

REFERENCES:

1. Halpin TC, Byrne WJ, Ament, ME: Colitis, persistent diarrhea and soy protein intolerance. *J Pediatr* 1977;91:404-407.
2. Ament ME, Rubin CE: Soy protein—another cause of the flat intestinal lesion. *Gastroenterology* 1972;62:227.
3. Iyngkaran N, Yadav M: Food Allergy, in Marsh MN (ed): *Immunopathology of the Small Intestine.* New York, John Wiley & Sons Ltd, 1987, p 421.
4. Eastham EJ, Lichauco T, Grady MI, et al: Antigenicity of infant formulas: Role of immature intestine on protein permeability. *J Pediatr* 1978;93(4):561-564.
5. Hill LW, Stuart HC: Soy bean food preparation for feeding infants with milk idiosyncrasy. *JAMA* 1929;93(13):985.
6. American Academy of Pediatrics Committee on Nutrition: Soy-protein formulas: Recommendations for use in infant feeding. *Pediatrics* 1983;72(3):359-363.
7. Bahna SL, Heiner DC: *Allergies to Milk.* New York, Grune & Stratton, 1980, p 127.
8. Businco L, Benincori N, Cantani A: Epidemiology, incidence and clinical aspects of food allergy. *Ann Allergy* 1984; 53:615-622.
9. Benkov KJ, LeLeiko NS: A rational approach to infant formulas. *Pediatr Ann* 1987;16(3):225-230.
10. Lothe L, Lindberg T, Jakobsson I: Cow's milk formula as a cause of infantile colic: A double-blind study. *Pediatrics* 1982;70:7-10.
11. May CD, Fomon SJ, Remigio L: Immunologic consequences of feeding infants cow milk and soy products. *Acta Paediatr Scand* 1982;71:43-51.

© 1988 Carnation Nutritional Products Printed in USA NP-009 9/88

Playground-Related Injuries in Preschool-Aged Children—United States, 1983-1987

FROM 1983 to 1987, nearly 6.72 million emergency room visits in the United States were for product-related injuries among preschool children 1-4 years old.* Approximately 305,000 (4.5%) of these injuries involved playground equipment. These playground equipment-related injuries occurred most frequently at home (38.3%), in sports or recreation settings (29.4%), or at school (8.9%). Of the 82,108 injuries in preschool-aged children attending day care (coded as occurring at school), 27,232 (33.2%) were related to playground equipment.

Most preschool-aged children with injuries involving school playground equipment were 3 or 4 years old and male. A higher proportion of playground-related injuries occurred in the spring than at other times of the year. Forty percent of playground-related injuries were associated with climbing apparatus, and two thirds of injuries were to the head and neck.

Lacerations (38.5%), contusions or abrasions (26.8%), fractures (16.8%), strains or sprains (4.4%), and concussions (1.7%) were most commonly reported. Head and neck injuries were primarily lacerations (55.7%) and contusions or abrasions (23.7%). Injury to the extremities and trunk included mostly fractures, contusions or abrasions, and strains or sprains (upper extremity—62.4%, 22.2%, and 12.2%; lower extremity—31.4%, 42.2%, and 15.4%; trunk—27.7%, 51.2%, and 9.2%, respectively). Approximately 5.3% of preschool-aged children treated in emergency rooms for playground-related injuries required hospitalization.

Reported by: Div of Injury Epidemiology and Control, Center for Environmental Health and Injury Control, CDC. (MMWR vol 37, No. 40)

CDC Editorial Note: By 1984, more than 11 million children attended day-care facilities.[1] The potential injury hazards of organized day care and day-care playgrounds have been documented.[2-5] The NEISS data suggest that further improvements in playground safety are needed to reduce playground-related injuries.

NEISS provides a data base for estimating injuries associated with playground equipment in young children in day-care facilities. However, these data are limited in that, by using "school" as the location to represent day-care playgrounds, they exclude children injured in day care at a home, church, or building other than a school. Conversely, some injuries that reportedly took place at school possibly occurred to children using a school playground but not attending day care. Interpreting these data is also difficult because the type, size, and cost of equipment at a school playground differ from those used in homes, churches, or private day care. Thus, the distribution by type of equipment in the overall day-care environment may vary considerably from that described here.

A CPSC-sponsored hazard analysis showed that falls to the ground surface account for 60% of playground equipment-related injuries.[6] A 1-foot fall directly on the head onto concrete or asphalt or a 4-foot fall onto packed earth can be fatal.[7-9] In contrast, surfaces made of energy-absorbing mats or loose materials such as wood chips or sand may reduce the likelihood of head injury even from falls of 8 feet.[7,8] Yet over 48% of day-care playground equipment is not installed over impact-absorbing surfaces.[2,3] Although in some cases the Occupational Safety and Health Administration requires that guard rails be installed to protect workers as low as 4 feet above ground level, no such protective legislation exists for children on playground equipment, some of which is more than 10 feet above the ground.[8]

Injury control programs should address the safety aspects of public and other playgrounds for all ages. According to NEISS data, 994,678 injuries in all age groups from 1983 to 1987 were associated with playground equipment; 243,807 (24.5%) of these injuries occurred at schools, and 257,070 (25.8%), at places of recreation. Recommendations to improve playground safety include installing playground equipment over energy-absorbing surfaces, locating the equipment away from obstructions, properly anchoring the equipment, checking the integrity of the equipment frequently, covering protrusions, removing broken equipment promptly, and instructing and supervising children in proper playground use.[10,11] If wood chips or sand are used as surfacing, they should be well maintained and not allowed to compact or fall below an adequate depth. Limiting the height of playground equipment may also be helpful. Parents should consider the safety aspects of playgrounds in day-care centers, schools, and public areas before allowing their children to use them.

References

1. The Child Day Care Infectious Disease Study Group. Public health considerations of infectious diseases in child day care centers. J Pediatr 1984;105:683-701.

2. O'Connor MA, Boyle WE Jr, O'Connor GT, Letellier R. Injury prevention practices in day-care centers. Presented at the 115th annual meeting of the American Public Health Association, New Orleans, Louisiana, October 18-22, 1987.

3. Davis WS, McCarthy PL. Safety in day-care centers (Abstract). Am J Dis Child 1988;142:386.

4. Aronson SS. Injuries in child care. Young Child 1983;38:19-20.

5. Landman PF, Landman GB. Accidental in-

juries in children in day-care centers. Am J Dis Child 1987;141:292-3.

6. Rutherford GW Jr. Injuries associated with public playground equipment. Washington, DC: US Consumer Product Safety Commission, 1978.

7. Mahajan BM, Beine WB. Impact attenuation performance of surfaces installed under playground equipment: report to the Consumer Product Safety Commission. Washington, DC: US Department of Commerce, National Bureau of Standards, Feb. 1979; publication no. NBSIR 79-1707.

8. Reichelderfer TE, Overbach A, Greensher J. Unsafe playgrounds (Letter). Pediatrics 1979;64:962-3.

9. Sweeney TB. X-rated playgrounds? (Letter). Pediatrics 1979;64:961.

10. US Consumer Product Safety Commission. A handbook for public playground safety: general guidelines for new and existing playgrounds. Vol I. Washington, DC: US Consumer Product Safety Commission, 1986.

11. US Consumer Product Safety Commission. Play happy, play safely: playground equipment guide for teachers, park and recreation directors, parents, youth leaders, and other concerned adults. Washington, DC: US Consumer Product Safety Commission, 1979.

*This estimate is based on data from the National Electronic Injury Surveillance System (NEISS) of the U.S. Consumer Product Safety Commission (CPSC). Sixty-two hospitals with emergency rooms located throughout the United States contribute to this data base. When weighted, the reports from NEISS reflect national estimates of persons with product-related injuries treated in hospital emergency rooms.

Sudden Infant Death Syndrome as a Cause of Premature Mortality—United States, 1984 and 1985

OF THE 10 leading causes of years of potential life lost before age 65 (YPLL), three occur primarily in the first year of life: congenital anomalies ranked fifth, prematurity ranked sixth, and sudden infant death syndrome (SIDS) ranked seventh.[1] This report, based on final mortality data, compares estimates of SIDS-associated YPLL by race and sex for 1984 and 1985 with those for 1980-1983.[2]

To estimate YPLL for SIDS as reported in Table V,[3] national death certificate data were compiled from the National Center for Health Statistics (NCHS), CDC, national mortality computer tapes. Deaths were attributed to SIDS if both the underlying cause of death was classified as category 798.0 (according to the International Classification of Diseases, Ninth Revision (ICD-9)) and the death occurred during infancy (less than 1 year of age). SIDS was divided into groups by race and sex of infant. YPLL was calculated by averaging the age at death for each subgroup for this study period.

In 1984, 5245 SIDS cases were reported, accounting for 339,517 YPLL (Table 1). Similarly, in 1985, 5315 SIDS deaths were reported, accounting for 344,114 YPLL. In both years, SIDS was the seventh leading cause of YPLL.[1]

Males accounted for 61% of SIDS-attributable YPLL for 1984-1985. Seventy percent of SIDS-attributable YPLL occurred among whites. The average annual YPLL rates per 1000 live births were highest for blacks and Native Americans (Table 2). However, rates for all racial/sex groups except white males and others (not including Native Americans) decreased slightly from those for 1980-1983.

Reported by: Pregnancy Epidemiology Br and Research and Statistics Br, Div of Reproductive Health, Center for Health Promotion and Education, CDC. (MMWR vol 37, No. 41)

CDC Editorial Note: Formerly called a "crib death" or "cot death," SIDS is now defined as "the sudden death of any infant or young child which is unexpected by history, and in which case a thorough postmortem examination fails to demonstrate an adequate cause of death".[4] Confirmation of SIDS requires a thorough history, a postmortem examination, and a death scene investigation.[5,6] In 1980, the SIDS autopsy rate by state ranged from 10% to 100% (median: 82%). By 1984, it had increased to 25%-100% (median: 92%), and by 1985, to 47%-100% (median: 93%). Appropriate investigation and diagnosis of SIDS may assist in allocating health-care resources for prevention programs.

References

1. CDC. Changes in premature mortality—United States, 1979-1986. MMWR 1988;37:47-8.

2. CDC. Premature mortality due to sudden infant death syndrome—United States, 1980-1986. MMWR 1987;36:236-8.

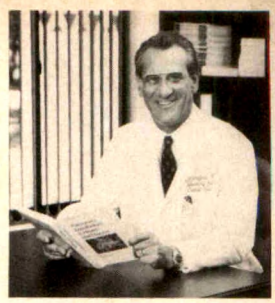
3. CDC. Introduction to Table V: premature deaths, monthly mortality, and monthly physician contacts—United States. MMWR 1982;31:109-10, 117.

4. Beckwith JB. Discussion of terminology and definition of sudden infant death syndrome. In: Bergman AB, Beckwith JB, Ray CG, eds. Sudden infant death syndrome. Proceedings of the Second International Conference on Causes of Sudden Death in Infants. Seattle, Washington: University of Washington Press, 1970.

5. Jones AM, Weston JT. The examination of the sudden infant death syndrome infant: investigative and autopsy protocols. J Forensic Sci 1976;21:833-41.

6. Lewman LV. Oregon's model system: a statewide approach. Pediatr Ann 1974;Nov:44-54.

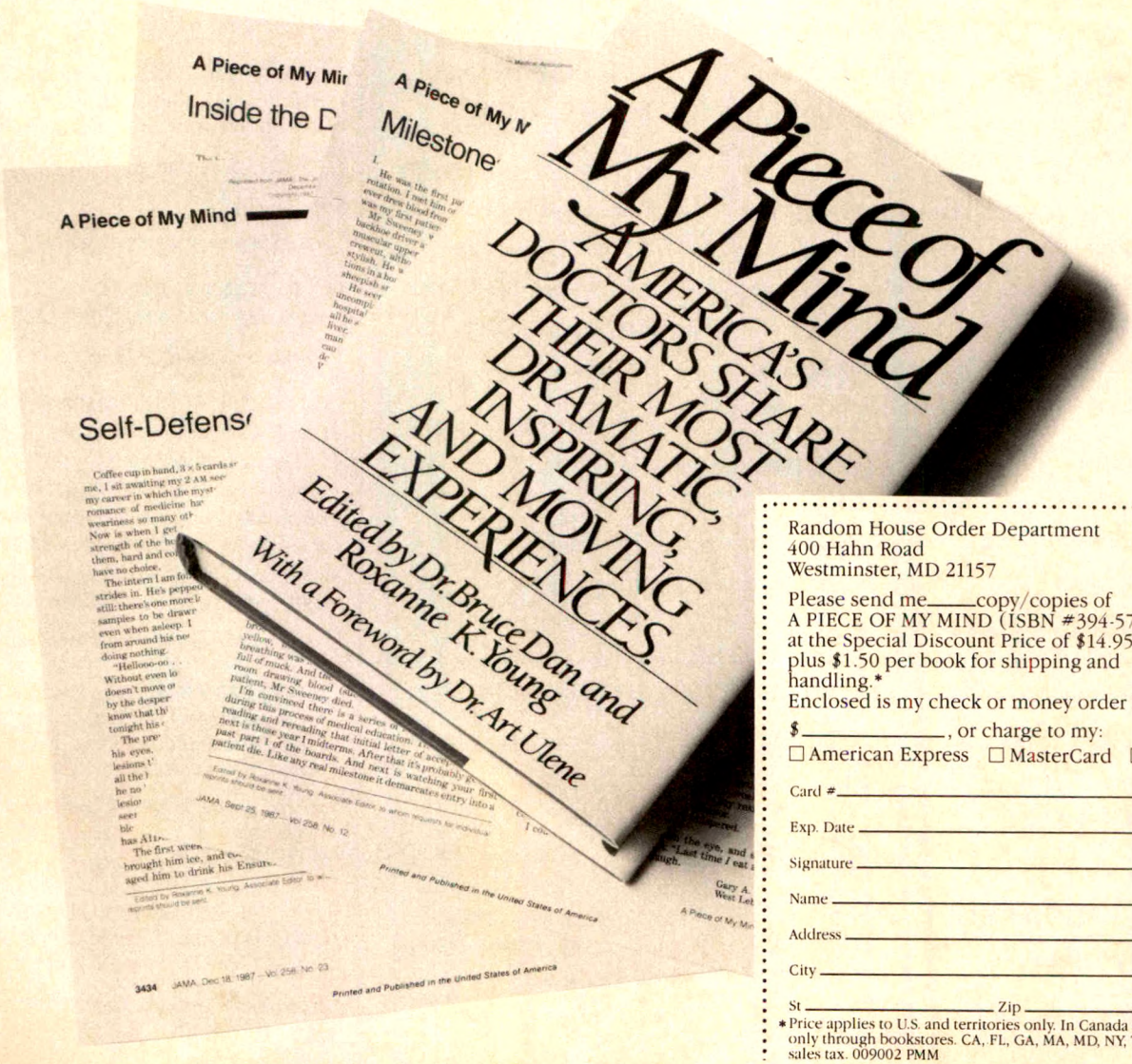
"Everything comes to a stop in my office until I've read A PIECE OF MY MIND in each new issue of JAMA."
W. G. Scoggins, MD



Now it's a book

The column you've loved for years is now collected in a handsomely bound hardcover book. Eighty extraordinary pieces, the best of the immensely popular A PIECE OF MY MIND columns from JAMA, are brought together for the first time. Relive the joys and sorrows of practicing medicine. Share the stories with your friends and loved ones.
ORDER GIFTS NOW FOR THE HOLIDAY SEASON.

Special Discount Physicians receive a $4.00 discount off the $18.95 cover price. You pay only $14.95 per copy plus shipping and handling. Call this toll-free number today, 1/800-638-6460 (in Maryland, 1/800-492-0782) Credit cards only. Or, if you prefer, send the coupon with your check. Allow 4 weeks for delivery.



Random House Order Department
400 Hahn Road
Westminster, MD 21157

Please send me____copy/copies of A PIECE OF MY MIND (ISBN #394-57715-9) at the Special Discount Price of $14.95 each plus $1.50 per book for shipping and handling.*
Enclosed is my check or money order for
$_____, or charge to my:
☐ American Express ☐ MasterCard ☐ Visa

Card #_____
Exp. Date_____
Signature_____
Name_____
Address_____
City_____
St_____ Zip_____

*Price applies to U.S. and territories only. In Canada available only through bookstores. CA, FL, GA, MA, MD, NY, TN, add sales tax. 009002 PMM

THE PEDIATRICS BOARD REVIEW COURSE

February 23-28, 1989 – Anaheim
April 6-12, 1989 – Nashville
May 26-31, 1989 – Louisville

Now, your only BOARD REVIEW just before Written and Oral Exams

OBJECTIVES:

- Improve basic and clinical knowledge in pediatrics
- Assist residents and fellows in organizing study
- Prepare candidates to take examinations
- Provide practicing pediatricians with a review and update

METHODS:

- HOME STUDY MATERIALS with a syllabus of questions and answers – and assignments
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

NEONATOLOGY
Growth and Development
Nutrition
Newborn Diseases
Fluids and Electrolytes
Critical Care

IMMUNOLOGY
Immune Physiology
Immunodeficiency
Allergy
Rheumatology

INFECTIOUS DISEASES
Bacterial Infections
Viral Infections
Spirchetes and Richettsia
Mychotic Infections
Parasitic Infections

CARDIOLOGY
Cardiac Evaluation
Cyanotic Diseases
Acyanotic Diseases
Acquired Diseases

GASTROENTEROLOGY
Oral Cavity/Esophagus
Anomalies and Diseases
Malabsorption
Liver and Gall Bladder
Pancreas

NEPHROLOGY
Renal Physiology
Glomerular Diseases
Congenital Uropathies
Urology

ENDOCRINOLOGY
Hypothalamus/Pituitary
Thyroid and Parathyroid
Adrenal Disorders
Gonadal Disorders
Diabetes/Hypoglycemia

HEMATOLOGY-ONC.
Red Cell Disorders
White Cell Disorders
Platelets and Coagulation
Solid Tumors

NEUROLOGY
Convulsive Disorders
Congenital Diseases
Acquired Diseases
Neuromuscular Diseases

PSYCHOLOGY
Psychological Development
Psychiatric Disorders
Child and Drug Abuse
Mental Retardation

GENETICS AND OTHER
Chromosomal Anomalies
Errors of Metabolism
Morphologic Syndromes
Preventive Medicine
Poisoning

OTHER SPECIALITIES
Orthopedics
Dermatology
Opthalmology
Otolaryngology
Pulmonology

Limited Enrollment: PEDIATRICS BOARD REVIEW REGISTRATION

Name _____

Address _____

City/State/Zip _____

Phone _____

For:
- ☐ February 23-28, 1989 – Anaheim
- ☐ April 6-12, 1989 – Nashville
- ☐ May 26-31, 1989 – Louisville
- ☐ Sept. 26-Oct. 1, 1989 – Chicago
- ☐ Check is enclosed for $
- ☐ Please send more information.

Mail today to:

1094 Dawn Lane
P.O. Box 2218
Terre Haute, IN 47802

*"Accommodations were comfortable..."**

GOALS AND LOCATION: The course is held the week before oral and written board exams. Sites are chosen for excellent study and minimal cost of hotel and travel for board candidates. Home study questions will be sent before the course. Your best value is to repeat the seminar for half price the week before both written and oral exams. Topics and faculty are upgraded for each program. Our hotel rates are typically $66 to $80 single and $80 to $98 double. Please wait for instructions before buying travel tickets.

*"...and those little extras...."**

LOWEST AIR FARES: Reliable Travel offers you the lowest air fare – often below super-saver rates. Please call toll-free 1-800-645-6504 ext. 10 and identify yourself with this Osler course for special group fares.

*"...remarkably complete and pleasant."**

PLACEMENT SERVICE: For a practice opportunity write or call (800) 356-7537.

*"...the most education for the money."**

FEES AND C.M.E. CREDITS:

- **C.M.E. Credit: 60 hrs.**
- Practicing Pediatrician: $630
- Residents and Fellows: $420
- Repeating course within 3 years: half price
- **Add 10% for Feb. '89 after Feb. 15, 1989.**
- Attendees not in course hotel add $8/day.
- $50.00 will reserve your position.

*"...home study material was extremely helpful."**

CANCELLATIONS: Refunds subject to $50 fee, will be made until the seminar begins.
- Cancellation after mailing home study material requires retention of half of the fee.

*"I feel [the course] helped me pass the boards."**

INFORMATION:

Joseph H. Selliken Jr., M.D.
THE OSLER INSTITUTE
1094 Dawn Lane, Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

**Comments by participants of our courses*

Published by the American Medical Association

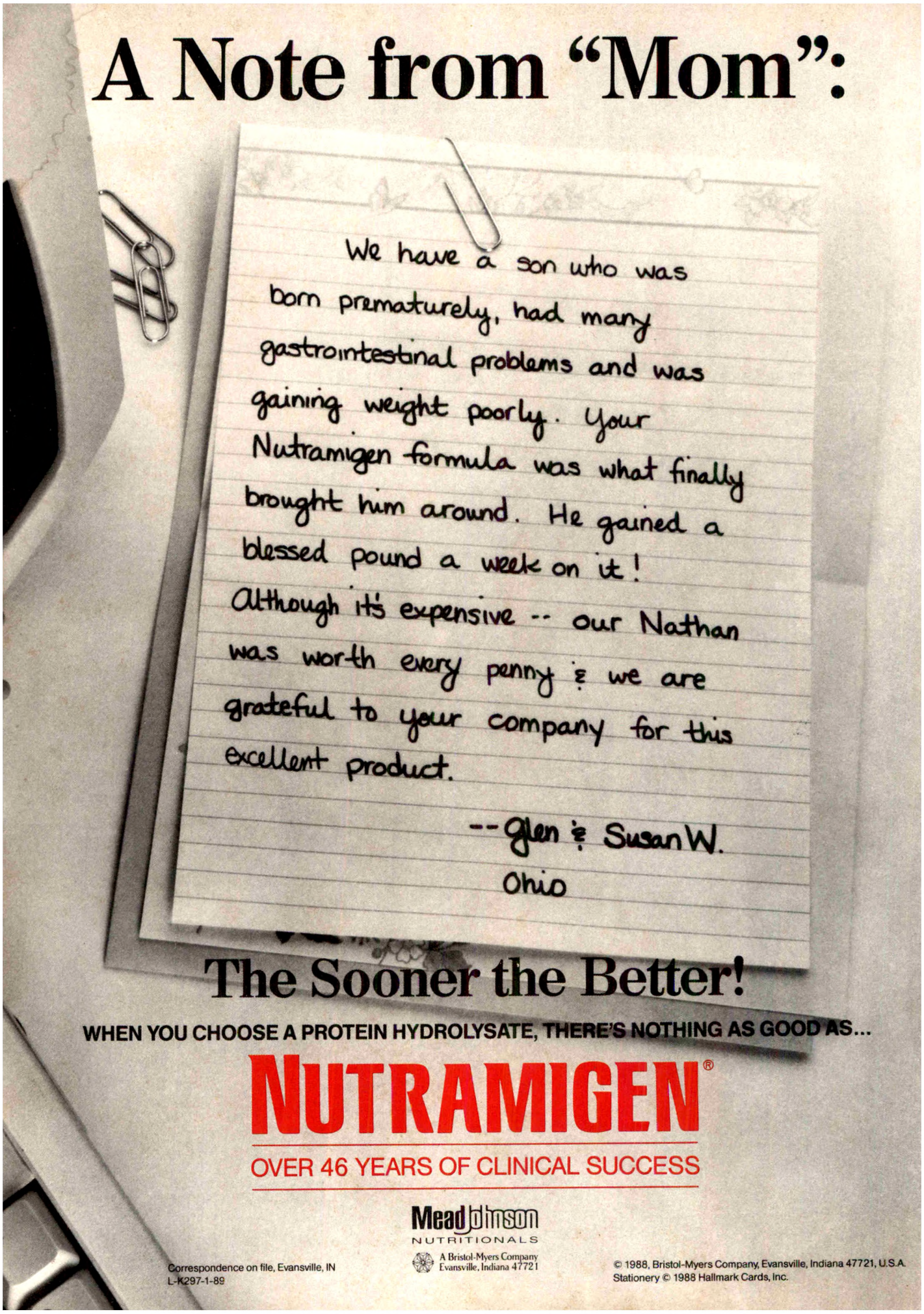
February 1989
Volume 143, Number 2

AJDC

AMERICAN JOURNAL OF DISEASES OF CHILDREN

THE PEDIATRIC FORUM		**137**
LEADS FROM THE MMWR		**145**
THE EDITORIAL BOARD SPEAKS . . . : Fetal Tissue Transplantation	*H. L. Nadler*	**149**
ARTICLES: Penicillin V Failure in Strep Pharyngitis	*M. A. Gerber et al*	**153**
Screening for Early Diagnosis of NEC	*H. W. Cheu et al*	**156**
Protein Intake and Renal Function in Children	*M. Nakano et al*	**160**
Nucleated RBC Levels in SGA Infants	*A. G. S. Philip et al*	**164**
PEDIATRIC PERSPECTIVES: Stress During Residency	*R. A. Hoekelman*	**177**
Resident Stress	*M. I. Cohen et al*	**181**
ARTICLES: Puberty in the Syndrome of Septo-optic Dysplasia	*C. E. Hanna et al*	**186**
Onset of Sperm Production in Pubertal Boys	*H. E. Kulin et al*	**190**
CT in Parietal Skull Fracture	*W. A. Bonadio et al*	**194**
SPORTS MEDICINE: Iron Deficiency in Athletes	*T. W. Rowland et al*	**197**
ARTICLES: Treatment of Postoperative Central Diabetes Insipidus	*J. A. McDonald et al*	**201**
Infection in Saudi Arabian Children With Sickle Cell Disease	*M. I. El Mouzan et al*	**205**
Efficacy and Safety of Home Nebulizer Therapy	*D. A. Zimo et al*	**208**
Exercise-Induced Cardiovascular Events	*F. W. Arensman et al*	**212**
EDUCATIONAL INTERVENTIONS: Career Direction of Primary Care Residents	*O. R. Mathieu, Jr, et al*	**217**
ARTICLES: Mortality Associated With Increasing Assisted Ventilation	*L. W. Doyle et al*	**223**
Airway Pathology After Ventilation	*M. J. Polak et al*	**228**
High-Frequency Jet Ventilation	*W. A. Carlo et al*	**233**
George Armstrong (1719-1787)	*H. Bloch*	**239**
THE *AJDC* ARCHIVES: Pediatric Biographies: George Armstrong	*J. Ruhräh*	**242**
Commentary	*V. A. Fulginiti*	**244**
SPECIAL FEATURES: Radiological Cases of the Month	*R. P. Davies et al*	**251**
	J. H. Truex et al	**253**
Picture of the Month	*P. R. Cohen et al*	**255**

A Note from "Mom":



The Sooner the Better!

WHEN YOU CHOOSE A PROTEIN HYDROLYSATE, THERE'S NOTHING AS GOOD AS...

NUTRAMIGEN®

OVER 46 YEARS OF CLINICAL SUCCESS

Mead Johnson
NUTRITIONALS
A Bristol-Myers Company
Evansville, Indiana 47721

Correspondence on file, Evansville, IN
L-K297-1-89

© 1988, Bristol-Myers Company, Evansville, Indiana 47721, U.S.A.
Stationery © 1988 Hallmark Cards, Inc.

Acc 27.3.89

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOL 143 NO. 2 FEBRUARY 1989

Copyright © 1989 by the American Medical Association

Monthly Circulation >44 500
Also published in French

THE PEDIATRIC FORUM

137 **What Causes Sexual Assault?** Lewis H. Margolis, MD, MPH, Linda Frankel, PhD, Ann Arbor, Mich; Pauline Bart, PhD, Chicago, Ill; Carole Jenny, MD, Seattle, Wash . . . **TEARS: Does Domestic Violence Play a Role?** Mary Rimsza, MD, Phoenix, Ariz . . . **Phenobarbital and Respiratory Complications in Neonates Receiving Mechanical Ventilatory Support** Mordechai Regev, MD, Ilan Arad, MD, Jerusalem, Israel . . . **A Patient With IgA Nephropathy** Steve Cachero, MD; James E. Springate, MD; Leonard G. Feld, MD, PhD, Buffalo, NY; Thomas R. Welch, MD; Annette Berry; A. James McAdams, MD, Cincinnati, Ohio . . . **Kawasaki Disease With Thrombocytosis Followed by Thrombocytopenia Purpura in the Same Patient** Robert N. Lipnick, MD, Naomi L. C. Luban, MD, Washington, DC . . . **Fructose-1,6-diphosphatase Deficiency: A 20-Year Follow-up** Orly N. Elpeleg, MD; Haggit Hurvitz, MD; David Branski, MD; Varda Barash, PhD, Jerusalem, Israel . . . **Pyloric Stenosis in Sick Premature Infants** Spencer W. Beasley, FRACS, John M. Hutson, MD, FRACS, Parkville, Australia; Jeffrey M. Perlman, MD, Richard J. Bower, MD, St Louis, Mo . . . **DICE: Nonclinical Causes of Overtreatment** Allan S. Cunningham, MD, Cooperstown, NY . . . **Hidden Salicylates** Prof Michael D. Szap, Brooklyn, NY

145 **LEADS FROM THE MMWR**

THE EDITORIAL BOARD SPEAKS . . .

149 **Fetal Tissue Transplantation**
Henry L. Nadler, MD, Chicago, Ill

ARTICLES

153 **Failure of Once-Daily Penicillin V Therapy for Streptococcal Pharyngitis**
Michael A. Gerber, MD; Martin F. Randolph, MD; Kathleen DeMeo; Henry M. Feder, Jr, MD, Farmington, Conn; Edward L. Kaplan, MD, Minneapolis, Minn

156 **Breath Hydrogen Excretion as a Screening Test for the Early Diagnosis of Necrotizing Enterocolitis**
Henry W. Cheu, MD; David R. Brown, MD; Marc I. Rowe, MD, Pittsburgh, Pa

160 **Protein Intake and Renal Function in Children**
Mitsuro Nakano, MD, PhD, Richmond, Va; Uri Alon, MD, Kansas City, Mo; Sandra S. Jennings, MS, RD, James C. M. Chan, MD, Richmond, Va

164 **Increased Nucleated Red Blood Cell Counts in Small for Gestational Age Infants With Very Low Birth Weight**
Alistair G. S. Philip, MD, FRCPE, Alison M. Tito, RNC, Portland, Me

PEDIATRIC PERSPECTIVES

177 **Stress Experienced During Pediatric Residency Training**
Robert A. Hoekelman, MD, Rochester, NY

181 **Patient Care, Resident Stress, and Government Regulation**
Michael I. Cohen, MD, Bronx, NY; Joseph Dancis, MD, New York, NY; Laurence Finberg, MD, Brooklyn, NY; Kurt Hirschhorn, MD, Michael Katz, MD, New York, NY; Edward Wasserman, MD, Valhalla, NY

Continued on p 131.

EDITORIAL BOARD

Editor

Vincent A. Fulginiti, MD
American Journal of Diseases of Children
PO Box 43700
Tucson, AZ 85733
(602) 626-4304

Associate Editors

James J. Corrigan, Jr, MD
Tucson, Ariz

Alan D. Bedrick, MD
Tucson, Ariz

Book Review Editor

Peggy C. Ferry, MD
Tucson, Ariz

Administrative Assistant

Joann M. Quane
Tucson, Ariz

Secretary

Laura Martin
Tucson, Ariz

Hugh D. Allen, MD, Columbus, Ohio
Milton I. Arnold, MD, Los Angeles, Calif
Richard W. Blumberg, MD, Atlanta, Georgia
Ben H. Brouhard, MD, Cleveland, Ohio
George W. Brown, MD, Los Lunas, NM
Beverly B. Dahms, MD, Cleveland, Ohio
Murray Feingold, MD, Boston, Mass
Patricia Ferrieri, MD, Minneapolis, Minn
Laurence Finberg, MD, Brooklyn, NY
Boyd W. Goetzman, MD, PhD, Davis, Calif
John D. Johnson, MD, Albuquerque, NM
James P. Keating, MD, St Louis, Mo
Elizabeth R. McAnarney, MD, Rochester, NY
Dan G. McNamara, MD, Houston, Tex
Beverly C. Morgan, MD, Orange, Calif
Henry L. Nadler, MD, Chicago, Ill
Robert Penny, MD, Los Angeles, Calif
Albert W. Pruitt, MD, Augusta, Ga
Kenneth B. Roberts, MD, Worcester, Mass
Barton D. Schmitt, MD, Denver, Colo
E. Richard Stiehm, MD, Los Angeles, Calif
William B. Strong, MD, Augusta, Ga
Beverly P. Wood, MD, Rochester, NY

Trust is more than a matter of taste.

Trust is knowing that your recommendation stands for efficacy. Dimetapp Elixir has a heritage of efficacy that's unsurpassed for colds and allergy relief. Every spoonful provides effective relief of the runny nose, sniffling and nasal congestion of a cold or flu. Dimetapp Elixir also relieves the itchy, watery eyes and sneezing of little allergy sufferers.

And, Dimetapp is a name that has always stood for great grape taste. So, compliance is never an issue. Trust Dimetapp Elixir. A heritage of efficacy in every good-tasting spoonful.

Dimetapp® Elixir

Nasal Decongestant/Antihistamine

A heritage of efficacy in every spoonful.

© 1989 A.H. Robins Company

Continued from p 129.

ARTICLES

186 Puberty in the Syndrome of Septo-optic Dysplasia
Cheryl E. Hanna, MD; Scott H. Mandel, MD; Stephen H. LaFranchi, MD, Portland, Ore

190 The Onset of Sperm Production in Pubertal Boys
Howard E. Kulin, MD; Miguel A. Frontera, MD; Laurence M. Demers, PhD; Mary J. Bartholomew, MS; Thomas A. Lloyd, PhD, Hershey, Pa

194 Clinical Indicators of Intracranial Lesion on Computed Tomographic Scan in Children With Parietal Skull Fracture
William A. Bonadio, MD; Douglas S. Smith, MD; Sylvia Hillman, MD, Milwaukee, Wis

SPORTS MEDICINE

197 Iron Deficiency in Athletes
Thomas W. Rowland, MD, John F. Kelleher, MD, Springfield, Mass

ARTICLES

201 Treatment of the Young Child With Postoperative Central Diabetes Insipidus
Jay A. McDonald, MD; Paul M. Martha, Jr, MD; James Kerrigan, MD; William L. Clarke, MD; Alan D. Rogol, MD, PhD; Robert M. Blizzard, MD, Charlottesville, Va

205 Infections and Sickle Cell Disease in Eastern Saudi Arabian Children
Mohamed I. El Mouzan, MD; Baker H. Al Awamy, MD; Gamil Absood, PhD, Dammam, Saudi Arabia

208 The Efficacy and Safety of Home Nebulizer Therapy for Children With Asthma
Deborah A. Zimo, MD; Michele Gaspar, RN; Javeed Akhter, MD, Chicago, Ill

212 Exercise-Induced Differences in Cardiac Output, Blood Pressure, and Systemic Vascular Resistance in a Healthy Biracial Population of 10-Year-Old Boys
Frederick W. Arensman, MD; Frank A. Treiber, PhD; Michael P. Gruber; William B. Strong, MD, Augusta, Ga

EDUCATIONAL INTERVENTIONS

217 Residency Training in General Pediatrics
Owen R. Mathieu, Jr, MD; Joel J. Alpert, MD; Stephen I. Pelton, MD, Boston, Mass

ARTICLES

223 Mortality With Increasing Assisted Ventilation of Very-Low-Birth-Weight Infants
Lex W. Doyle, MB, BS, Parkville, Australia; Laurence J. Murton, MB, BS, Carlton, Australia; William H. Kitchen, MD, Parkville, Australia

228 Comparison of Airway Pathologic Lesions After High-Frequency Jet or Conventional Ventilation
Mark J. Polak, MD; William H. Donnelly, MD; Richard L. Bucciarelli, MD, Gainesville, Fla

233 High-Frequency Jet Ventilation in Neonatal Pulmonary Hypertension
Waldemar A. Carlo, MD; Aris Beoglos, RN, MSN; Robert L. Chatburn, RRT; Michele C. Walsh, MD; Richard J. Martin, MD, Cleveland, Ohio

Continued on p 132.

The AMERICAN JOURNAL OF DISEASES OF CHILDREN is a member of the consortium of AMA journals listed below. The Archives reaches more than 41 500 readers in 85 countries each month. The complete text of all AMA journals is available on the MEDIS data base from Mead Data Central, Dayton, Ohio.

JAMA The Journal of the American Medical Association

AJDC American Journal of Diseases of Children

archives of **Dermatology**

archives of **General Psychiatry**

archives of **Internal Medicine**

archives of **Neurology**

archives of **Ophthalmology**

archives of **Otolaryngology-Head & Neck Surgery**

archives of **Pathology & Laboratory Medicine**

archives of **Surgery**

James H. Sammons, MD, Executive Vice-President

James S. Todd, MD, Senior Deputy Executive Vice-President

Kenneth E. Monroe, Deputy Executive Vice-President

Theodore R. Chilcoat, Jr, Assistant Executive Vice-President

M. Roy Schwarz, MD, Assistant Executive Vice-President

George D. Lundberg, MD, Vice-President, Scientific Information

John T. Baker, Vice-President, Publishing

Norman D. Richey, Director, Publication Production and Printing Division

Lee A. Parent, Director, Circulation-Fulfillment Division

Dennis Joseph Dennehy, Director, Advertising Sales and Promotion Services Division

Thomas J. Carroll, Director, Department of Advertising Communication

Raymond Christian, Director, Advertising Services Department

PUBLICATION STAFF
Offices: 535 N Dearborn St
Chicago, IL 60610

Managing Editor and Director, AMA Specialty Journals:
Michael D. Springer

Associate Editor:
Julie Foreman

Production Manager:
Marlene M. Hinsch

Assistant Production Manager:
John R. Sayban

Editorial Processing Manager:
Cheryl Iverson

Assistant Editorial Processing Manager:
Paula Glitman

Permissions and Graphic Design Manager:
Dennis J. Shipley

Staff Assistants:
Diane Darnell
Bonnie Van Cleven

Copy Editing:
Patricia A. Predey (Supervisor)
Vickey Golden (Free-lance Coordinator)
Paul Frank (Senior Copy Editor)
Stephen Borysewicz
John Radanovich

Production Supervisors:
Betty Frigerio (Advertising)
Thomas J. Handrigan (Illustrations)
Elizabeth Petrikenas (Proofreading)
Mary C. Steermann (Editorial)
JoAnne Weiskopf (Layout)

Proofreading:
Teresa H. Omiotek
Richard T. Porter
Jennifer Reiling
Barbara Wojtowicz

Art and Senior Production Assistants:
Melinda Arcabos
Cari Biamonte
Laura Bleiler
Karen Branham
Cynthia Gelper
Jerri Hall-Gortowski
Anita Henderson
Debra Lucas
Kimberly McCormick
Juliana K. Mills
Dorothy Patterson
Susan Price
E. Ruth White
Ellen Yoshihara

Production Assistant:
Darlene E. Filips

Editorial Assistant:
Jean Schaffner

Department of Scientific and Socioeconomic Indexing:
Norman Frankel (Director)
George Kruto
Mary Kay Tinerella
Susan McClelland

Please address communications concerning accepted or published communications to AMA Specialty Journals, 535 N Dearborn St, Chicago, IL 60610.

EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

Continued from p 131.

239 George Armstrong (1719-1787)
Harry Bloch, MD, New York, NY

THE *AJDC* ARCHIVES

242 Pediatric Biographies: George Armstrong
John Ruhräh, MD, Baltimore, Md

244 Commentary
Vincent A. Fulginiti, MD, Tucson, Ariz

SPECIAL FEATURES

Radiological Cases of the Month

251 Roger Philip Davies, MB, BS,
Kazimierz Kozlowski, MD (*Contributors*), Sydney, Australia;
Beverly P. Wood, MD (*Section Editor*), Rochester, NY

253 Jonathan Holt Truex, PhD, MD,
Teresa L. Silberman, MD (*Contributors*), Marshfield, Wis;
Beverly P. Wood, MD (*Section Editor*), Rochester, NY

255 Picture of the Month
Philip R. Cohen, MD; Vincent P. Beltrani, MD;
Gregory L. Zalar, MD (*Contributors*), New York, NY;
Murray Feingold, MD (*Section Editor*), Brighton, Mass

BOOK REVIEW

Paediatric Trauma (Alpar, Owens, eds) Reviewed by
Martha Bushore, MD, West Palm Beach, Fla (p 169)

134 INDEX TO ADVERTISERS

136 INSTRUCTIONS FOR AUTHORS

AJDC, American Journal of Diseases of Children (ISSN 0002-922X) is published monthly by the American Medical Association, 535 N Dearborn St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

SUBSCRIPTION RATES—The subscription rates for the American Journal of Diseases of Children are as follows: $48 for one year, $81 for two years in the United States and US Possessions; all other countries, one year, $58; two years, $101 for surface delivery. (For expedited air delivery to most countries, add $15 surcharge for one year subscription, $30 for two years.) Rates for subscriptions for delivery to Japan or South Korea are available through exclusive agents—contact the publisher. ***Special rates for residents and medical students in the United States and US Possessions are available.*** Address inquiries to the American Medical Association, Circulation and Fulfillment Division, 535 N Dearborn St, Chicago, IL 60610. Phone: (312) 280-7168.

CHANGE OF ADDRESS—POSTMASTER, send all address changes for AJDC, American Journal of Diseases of Children to Caryl L. Wertheimer, Director of Fulfillment, 535 N Dearborn St, Chicago, IL 60610. Notification of address change must be made at least six weeks in advance, include both old and new addresses, a recent mailing label, and your new zip code.

ADVERTISING OFFICES: Eastern: 600 Third Ave, Suite 3700, New York, NY 10016 (**Manager:** Robert C. Corcoran [212-867-6640]; **Representative:** Phillip B. Altamore); **Midwest/Farwest:** 535 N Dearborn St, Chicago, IL 60610 (**Manager:** Thomas J. Carroll [312-280-7182]; **Representatives:** John P. Cahill, Midwest; Daniel T. Mjölsness, Farwest)

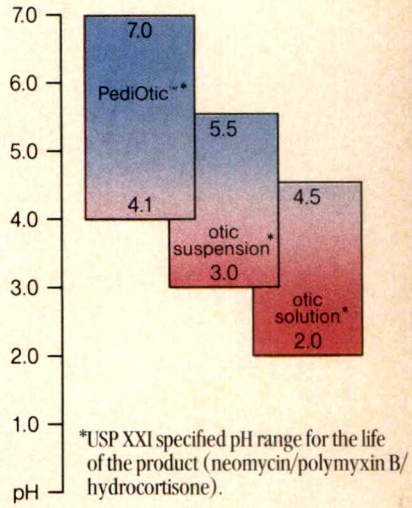
Advertising Principles: Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.

NEW

PediOtic™ suspension sterile

Formulated to be less acidic to help minimize irritation.

A more normal pH range means less potential for painful irritation.



*USP XXI specified pH range for the life of the product (neomycin/polymyxin B/hydrocortisone).

Formulated to help take the sting out of otitis externa therapy

New PediOtic™ suspension is specially formulated to have a higher pH range than conventional otics.

Children may be less likely to resist its instillation, and their parents will appreciate the ease of compliance.

And you can prescribe new PediOtic suspension with confidence, knowing it contains the same proven antibiotic/anti-inflammatory combination physicians have trusted for years.

Now there's a gentle effective treatment for "swimmer's ear" to please patient, parent, *and* physician.

Please see brief summary of prescribing information on next page.

PediOtic™ suspension sterile

Wellcome

(polymyxin B sulfate-neomycin sulfate-hydrocortisone)

NEW

PediOtic™ suspension sterile

(polymyxin B sulfate-neomycin sulfate-hydrocortisone)

DESCRIPTION: Pediotic suspension (polymyxin B sulfate-neomycin sulfate-hydrocortisone) is a sterile antibacterial and anti-inflammatory suspension for otic use. Each ml contains: Aerosporin® (polymyxin B sulfate) 10,000 units, neomycin sulfate equivalent to 3.5 mg neomycin base, and hydrocortisone 10 mg (1%). The vehicle contains thimerosal 0.001% (added as a preservative) and the inactive ingredients cetyl alcohol, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, propylene glycol, and Water for Injection. Sulfuric acid may be added to adjust pH. Pediotic suspension has a minimum pH of 4.1, which is less acidic than the minimum pH of 3.0 for Cortisporin® Otic Suspension.

INDICATIONS AND USAGE: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia, and varicella infections.

WARNINGS: This product should be used with care in cases of perforated eardrum and in longstanding cases of chronic otitis media because of the possibility of ototoxicity. Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known. When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

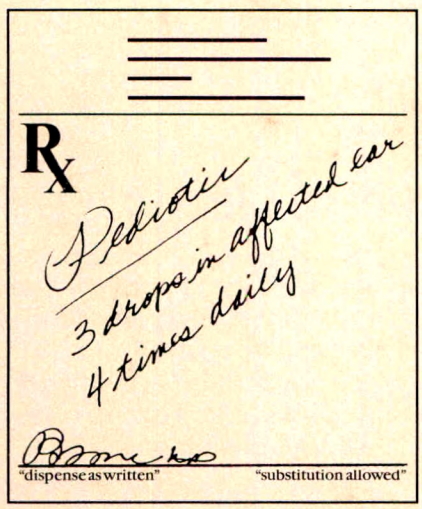
ADVERSE REACTIONS: Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported (see WARNINGS section). Adverse reactions have occurred with topical use of antibiotic combinations including neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in two of 2,175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]

The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. Stinging and burning have been reported rarely when this drug gained access to the middle ear.

HOW SUPPLIED: Bottle of 7.5 ml with sterilized dropper. NDC 0081-0910-02. Store at 15° to 25°C (59° to 77°F).

REFERENCES: 1. Leyden JJ, Kligman AM: Contact dermatitis to neomycin sulfate. *JAMA* 1979;242:1276-1278. 2. Prystowsky SD, Allen AM, Smith RW, et al: Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. *Arch Dermatol* 1979;115:959-962.

BURROUGHS WELLCOME CO., Research Triangle Park, NC 27709
Copr. © 1988 Burroughs Wellcome Co. All rights reserved. PED-101



Formulated to help take the sting out of otitis externa therapy.

INDEX TO ADVERTISERS

Abbott Laboratories 245-246
Allen & Hanburys, Division of Glaxo, Inc. 135, 216A-B

Burroughs Wellcome Company 133-134

Carnation Company 136A-H, 174-176, 249
Connaught Laboratories, Inc. 184A-D, 185, 220-222

Fisons Corporation 257-258
Forest Pharmaceuticals, Inc. 173, 247

ICN Pharmaceuticals, Inc. 200A-D

McNeil Consumer Products Company ..... Cover 3
Mead Johnson Nutritional Division ..... Cover 2

National Biological Corporation 246
National Institutes of Health 173

Osler Institute 260

Permanente Medical Group 172
Praxis Biologics 152A-D

Richardson-Vicks, Inc. 183
A.H. Robins Company 130, 250
Rorer Pharmaceuticals 147-148

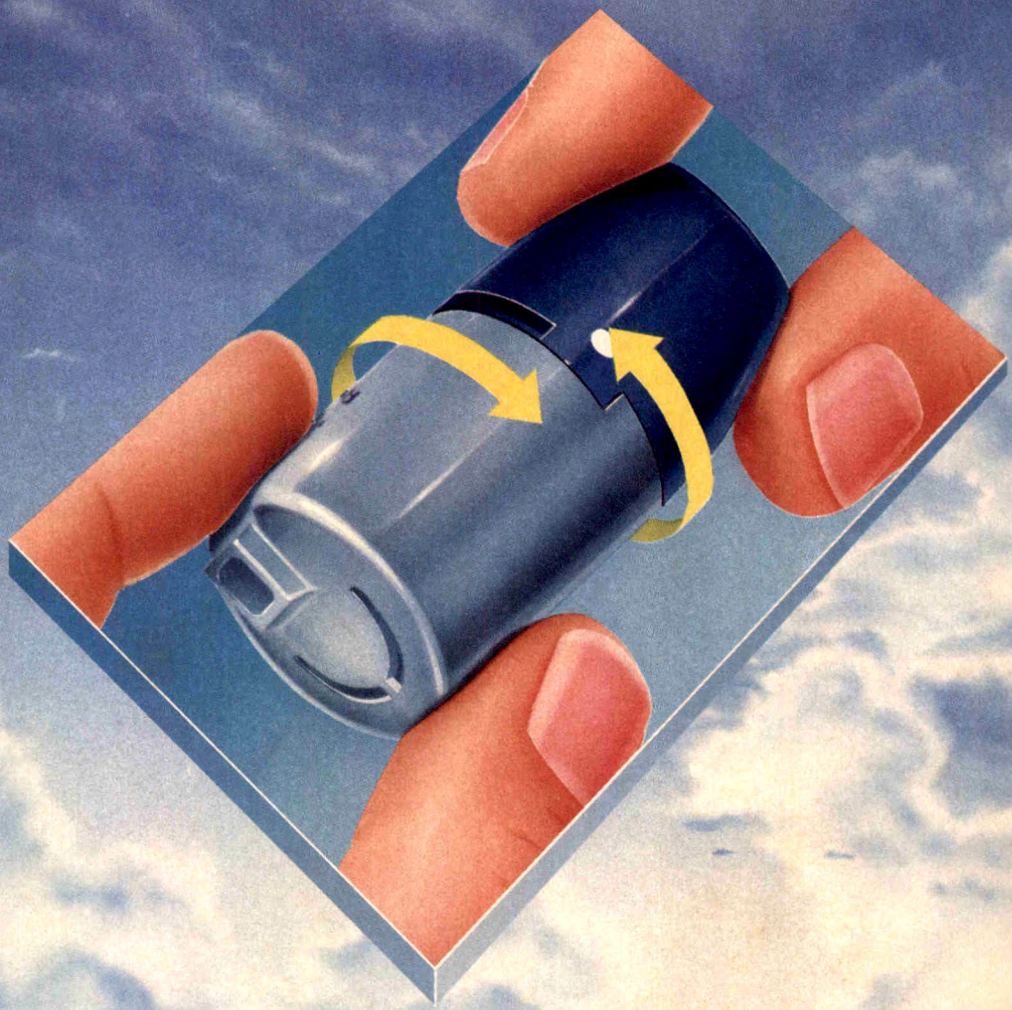
Sandoz Pharmaceuticals Corporation 143, 151-152, 259
E.R. Squibb & Sons, Inc. 170-172

University of Alabama 172

Wyeth-Ayerst Laboratories ..... 144, Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

COMING SOON...



NEW **VENTOLIN ROTACAPS®** FOR INHALATION
(ALBUTEROL SULFATE)
AND
ROTAHALER® INHALATION DEVICE

Exclusively from
Allen & Hanburys™
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

Printed in USA
VIN 362

September 1988

Instructions for Authors

NEW MANUSCRIPT PROCEDURE

On Jan 1, 1988, *AJDC* initiated a new procedure. Manuscripts submitted to *AJDC* will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information.—Please send manuscripts and correspondence by first-class mail (*do not use registered, certified, or express mail*) to the Editor, Vincent A. Fulginiti, MD, *AJDC*, PO Box 43700, Tucson, AZ 85733. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval *if requested* by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

Step 1.—*Cover Letter.*—All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNATURES):

1. *Copyright Release.*—"In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA."

2. *Statement of Affirmation.*—"This manuscript has not been published anywhere in any language and is not under simultaneous consideration by another publication. This manuscript is original and ALL authors have seen and approve of its contents."

3. *Financial Disclosure.*—List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg, employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of *AJDC*.

Step 2.—*Manuscript Format.*—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. *Do not use justified right margins.*

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with *each line, including headings, double-spaced.* Continuations should be on a second sheet with all headings repeated.

9. Use Système International (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed *label* and affixed on the back of each illustration. *Do not write directly on the print.*

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies or color prints. Fee is $400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from *both* parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, Williams E. Persistent fetal circulation: neurodevelopment outcome. *AJDC.* 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P. Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty. In: Conly J, Dickinson JT, eds. *Plastic and Reconstructive Surgery of the Face and Neck.* New York, NY: Grune & Stratton; 1972:84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.

13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from *publisher* and *author.* Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3.—*Special Departments.*—Criteria for several special departments are given below.

1. *The Pediatric Forum.*—This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC.* The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. *From Research to Relevance.*—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. *Educational Interventions.*—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

4. *Sports Medicine.*—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
- ____ 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors.
- ____ 3. Original typed manuscript plus three copies.
- ____ 4. Triple-spacing; double-spacing for tables and legends.
- ____ 5. Right margins UNJUSTIFIED.
- ____ 6. Title 75 characters or less.
- ____ 7. Abstract included.
- ____ 8. References in proper format, cited in numerical order.
- ____ 9. Four sets of illustrations.
- ____ 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- ____ 12. Permission forms for illustrations previously published elsewhere.

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

What Causes Sexual Assault?

Sir.—The article by Jenny[1] in the July 1988 issue of *AJDC* represents a disturbing setback in our understanding of sexual assault that has developed over the past 20 years.[2] The focus on "risk-taking" behaviors such as alcohol use or agreeing to go into a car or house with a recent acquaintance implies that these women caused or were to blame for their assaults. Is it not self-evident that those who committed the assaults were also out after 10 PM or that they were also probably using drugs? Is it not painfully clear that none of these behaviors justifies assault of a young woman by a man?

Risk-taking behaviors are unwise for a variety of reasons, not the least of which is that young women who drink or stay out late are more likely to run into men who may assault them. Nevertheless, such behaviors do not mean that these young women caused their assaults. Consequently, Jenny's public policy prescriptions are misplaced. Controlling the behavior of women out of concern for their safety inevitably leads to limitations on their opportunities for economic advancement.[3] Curfews or restrictions on alcohol for those who assault others, instead of the victims, might be effective and justified. Examination of the antecedents of assault among those who commit assaults might be worthwhile and might point to possible prevention strategies. Another potential public policy would be to make improvements in public transportation so that young women are not obliged to take rides with acquaintances under circumstances that they would prefer to avoid. Focusing, however, on the psychological characteristics of women victims—as if those characteristics caused the assaults—seems pointless, if not harmful.

We agree that "the end result of sexual violence is a devastated young woman who feels vulnerable and out of control of her body and environment."[1(p772)] Unfortunately, as long as physicians, through their research, and our culture, through a variety of practices,[4] blame the victims of these terrible crimes, we are unlikely to make much progress in their prevention.

LEWIS H. MARGOLIS, MD, MPH
School of Public Health
University of Michigan
1420 Washington Heights
Ann Arbor, MI 48109-2029

LINDA FRANKEL, PHD
Residential College
University of Michigan
Ann Arbor, MI 48109-1245

PAULINE BART, PHD
Department of Psychiatry
University of Illinois
at Chicago
Chicago, IL 60612

1. Jenny C: Adolescent risk-taking behavior and the occurrence of sexual assault. *AJDC* 1988;142:770-772.
2. Bart PB, O'Brien PH: *Stopping Rape: Successful Survival Strategies.* Elmsford, NY, Pergamon Press Inc, 1985.
3. Rothman S: *Women's Proper Place.* New York, Basic Books Inc Publishers, 1978.
4. Brownmiller S: *Against Our Will: Men, Women, and Rape.* New York, Simon & Schuster Inc Publishers, 1975.

In Reply.—Dr Margolis and his colleagues miss a major point of the article. I examined antecedent behaviors, not to lay blame on the victims for past assaults, but to develop strategies to prevent *future* sexual assaults.

The issues in preventing adolescent and adult sexual assault are similar to those that have been described in child sexual assaults. Prevention efforts can focus on incarcerating and/or treating the offender or improving the mental health of potential offenders; improving the effectiveness of the criminal justice system, which, it is hoped, acts as a deterrent; improving the community environment, providing safe housing, safe transportation, and adequate street lighting; and increasing the protective behaviors of the individual to decrease their likelihood of victimization.[1]

As health care providers, we can have influence in all these areas but are most likely to affect the last category.

The role of women in our society has changed drastically. These changes have led to equality, independence, and opportunities for women. The changes also have led to increased personal risk. Women are less safe as they become independent and self-sufficient. As long as society cannot guarantee safety for girls and women, it is important for them to understand how to decrease their risk of assault.

I have evaluated and treated hundreds of adolescent sexual assault victims. My overwhelming sense is that much of this misery could have been prevented. Prevention is a very different concept from blame.

Assailants need to be accountable for their heinous actions, but we do adolescents a disservice by not informing them of the risks associated with various life-styles.

CAROLE JENNY, MD
Department of Pediatrics and
Sexual Assault Center
Harborview Medical Center
325 Ninth Ave
Seattle, WA 98104

1. Finkelhor D: *Child Sexual Abuse.* New York, Free Press, 1984.

TEARS: Does Domestic Violence Play a Role?

Sir.—In the May 1988 issue of *AJDC*, Garza and colleagues[1] report on the epidemiology of the early amnion rupture spectrum of defects (TEARS). One of their conclusions is that young, black, multigravida mothers are at increased risk for having newborns with these defects. They suggest that the higher prevalence of TEARS among this group may be due to ascertainment bias.

Although the primary cause of the early amnion rupture spectrum remains idiopathic, at least some cases have been attributed to trauma.[2] It is interesting to note that the group with the highest prevalence of TEARS is also a group that is at higher risk for maternal trauma due to domestic violence. In a prevalence study of domestic violence during pregnancy, Helton et al[3] found that 8% of women gave a history of battering during their current pregnancy. The women who were battered during pregnancy were younger than the nonbattered women and black women reported being bat-

tered more often than women of other racial or ethnic groups.

Risk factors for domestic violence include lower socioeconomic status, family stress, social isolation, and violent childhoods. Certainly pregnancy is a time of increased family stress, perhaps more so for the multigravida mother. Is it possible that the higher prevalence of TEARS at the hospital that serves groups of lower socioeconomic status and the increased incidence of TEARS in Atlanta among young black multigravida mothers is due to domestic violence? It would be of interest to interview retrospectively the Atlanta mothers regarding domestic violence or other trauma during pregnancy.

Domestic violence in our society is, unfortunately, common and greatly underreported. Child abuse often begins in utero. The possibility that TEARS as well as other adverse fetal outcomes may be due to this violence requires further study.

MARY RIMSZA, MD
Department of Pediatrics
Maricopa Medical Center
Phoenix, AZ 85010

1. Garza A, Cordero JF, Mulinare J: Epidemiology of the early amnion rupture spectrum of defects. *AJDC* 1988;142:541-544.

2. Jones KL: *Smith's Recognizable Patterns of Human Malformation*, ed 4. Philadelphia, WB Saunders Co, 1988, pp 576-583.

3. Helton AS, McFarlane J, Andersen ET: Battered and pregnant: A prevalence study. *Am J Public Health* 1987;77:1337-1339.

Phenobarbital and Respiratory Complications in Neonates Receiving Mechanical Ventilatory Support

Sir.—Kuban et al[1] have reported an increased occurrence of pneumothorax and interstitial emphysema in infants of low birth weight receiving mechanical ventilatory support who also received phenobarbital sodium as prophylaxis for intraventricular hemorrhage. No reference was made, however, to the possibility of such an association in term infants.

Phenobarbital is routinely used in our unit to treat neonatal seizures occurring after severe perinatal asphyxia.[2] Since mechanical ventilatory support is often applied in such instances to prevent brain swelling or to treat associated lung disease, we decided to review the records of such term infants for the occurrence of iatrogenic pulmonary complications.

During the past seven years, 11 neonates received phenobarbital in our unit while receiving mechanical ventilatory support without having prior iatrogenic respiratory complications. Gestational ages ranged from 37 to 42 weeks and birth weights ranged from 2060 to 4700 g. All of the infants suffered from severe perinatal asphyxia with initial Apgar scores of 0 in eight instances and with an initial blood pH of less than 7.0 in six infants and less than 7.17 in the other infants. Ten infants received phenobarbital sodium for actual seizures while the 11th received it as prophylaxis during muscle paralysis. The loading dose was 10 to 20 mg/kg given intravenously with a maintenance dose of 5 mg/kg/d. Eight patients received the drug on the first day of life. Mechanical ventilatory support was started on the first day of life for protection against brain edema in most cases. Three infants had associated meconium aspiration syndrome, one had persistent pulmonary hypertension of the newborn, and one was eventually diagnosed as suffering from Werdnig-Hoffman disease. Artificial ventilatory support was given for at least 24 hours with a mean duration of 43 days (range, one to 15 days), a mean maximal inspiratory pressure of 28.9 cm H_2O (range, 15 to 50 cm H_2O), and a mean maximal respiratory rate of 78/min (range, 18 to 180/min).

Five patients eventually died. We found no case in which a pneumothorax occurred or any other air-leak phenomena developed.

Though limited, our data seem to indicate that there is no increased risk for respiratory complications associated with the administration of phenobarbital to term infants receiving mechanical ventilatory support.

MORDECHAI REGEV, MD
ILAN ARAD, MD
NICU, Department of Pediatrics
Hadassah University Hospital
Mt Scopus
Jerusalem 91240, Israel

1. Kuban KCK, Leviton A, Brown ER, et al: Respiratory complications in low-birth-weight infants who received phenobarbital. *AJDC* 1987; 141:996-999.

2. Volpe JJ: Neonatal seizures, in Volpe JJ (ed): *Neurology of the Newborn.* Philadelphia, WB Saunders Co, 1987, pp 129-158.

A Patient with IgA Nephropathy

Sir.—The recent article by Welch et al[1] describing five children with rapidly progressive IgA nephropathy prompted us to report the following case.

Patient Report.—A 16-year-old girl presented with a two-week history of headache, nausea, and blurred vision. Her medical history was significant for idiopathic mental retardation, cerebral palsy, and recurrent urinary tract infections. Episodes of gross hematuria or symptoms suggestive of Henoch-Schönlein purpura were denied. Three years earlier, a blood pressure of 100/70 mm Hg and proteinuria (3+) had been noted; results of an intravenous pyelogram and voiding cystourethrogram performed at that time were normal.

Examination revealed an anxious, confused girl with a blood pressure of 240/160 mm Hg. Bilateral grade IV hypertensive retinopathy was present. Urinalysis showed proteinuria (4+) without red blood cells. Urine protein excretion was 5.3 g/d. Her serum creatinine concentration was 133 μmol/L, and the albumin concentration was 22 g/L. Serum complement levels and results of liver function tests and serologic studies for systemic lupus were normal. Renal sonography, dimercaptosuccinic acid scanning, and arteriography revealed no evidence for reflux nephropathy or renal artery stenosis. A renal biopsy specimen showed complete or partial sclerosis of 50% of glomeruli. The remaining glomeruli manifested focal mesangial expansion and proliferation. Crescents were not observed. Immunofluorescent microscopy revealed diffuse mesangial IgA deposition, and numerous mesangial deposits were found by electron microscopy. In spite of appropriate antihypertensive therapy, end-stage renal failure developed 20 months after presentation.

Comment.—Clearly, the clinical features and natural history of IgA nephropathy are remarkably diverse. Isolated proteinuria and malignant hypertension are uncommon but well-documented manifestations of this disease.[2-5]

STEVE CACHERO, MD
JAMES E. SPRINGATE, MD
LEONARD G. FELD, MD, PHD
Division of Nephrology
The Children's Hospital
219 Bryant St
Buffalo, NY 14222

1. Welch TR, McAdams AJ, Berry A: Rapidly progressive IgA nephropahty. *AJDC* 1988;142: 789-793

2. Yoshikawa N, Ito H, Yoshiara S, et al: Clinical course of immunoglobulin A nephropathy in children. *J Pediatr* 1987;110:555-560.

3. Nakayama M, Hara M, Kuwahara K, et al: A case of IgA nephropathy associated with malignant hypertension and cerebral hemorrhage. *Jrn J Nephrol* 1985;27:859-863.

4. Perez-Fontan M, Miguel JL, Picazo ML, et al: Idiopathic IgA nephropathy presenting as malignant hypertension. *Am J Nephrol* 1986;6: 482-486.

5. Subias R, Botey A, Darnell A, et al: Malignant or accelerated hypertension in IgA nephropathy. *Clin Nephrol* 1987;27:1-7

In Reply.—The patient report by Cachero et al illustrates two interesting points about the development of end-stage renal disease in IgA nephropa-

thy. First, it points out the important negative prognostic significance of hypertension and heavy proteinuria. As Cachero et al mention, this observation has been made in other series of patients. Although recurrent gross hematuria is often regarded as the hallmark of IgA nephropathy, the disease may occur in the total absence of hematuria.

This patient report also demonstrates that end-stage renal disease can evolve in IgA nephropathy in the absence of crescents. Patients such as the five we described, with crescenteric nephritis and rapid deterioration, are probably not typical. The child described by Cachero et al, in whom there was about a five-year course before end-stage renal disease occurred, probably represents a more usual situation. This is the type of natural history described by Droz,[1] in whose series there was a steady 2.5% annual risk of renal failure over a 20-year period.

THOMAS R. WELCH, MD
ANNETTE BERRY
Division of Nephrology
A. JAMES MCADAMS, MD
Division of Pathology
Children's Hospital
Research Foundation
Elland and Bethesda avenues
Cincinnati, OH 45229-2899

1. Droz D: Natural history of primary glomerulonephritis with mesangial deposits of IgA. *Contrib Nephrol* 1976;2:150-157.

Kawasaki Disease With Thrombocytosis Followed by Thrombocytopenia Purpura in the Same Patient

Sir.—Kawasaki disease has been commonly associated with numerous hematologic abnormalities, including anemia, leukocytosis, thrombocytosis, and enhanced platelet aggregation.[1] However, thrombocytopenia has, to our knowledge, not been previously described. We describe a patient with Kawasaki disease who developed idiopathic thrombocytopenia purpura (ITP).

Patient Report.—A 9-year-old boy was in excellent health until he presented with an erythematous rash and spiking fever of six days' duration, arthralgias involving his hips and ankles, headache, and sore throat. The patient denied any history of cough, rhinorrhea, shortness of breath, nausea, vomiting, or other complaints. He had moved to the area from Colorado two weeks prior to admission and denied contact with any animals, chemicals, or other substances. The patient's medical history was unremarkable and he reported no allergies. The patient was admitted to the hospital and treated with cefuroxime for two days, but continued with high intermittent fever and was transferred to Children's Hospital National Medical Center, Washington, DC.

On examination, the patient was in moderate discomfort with a papular erythematous rash over his trunk and extremities. His lips were dry and had mild fissuring. The pharynx was hyperemic and hypertrophy of tongue papillae (strawberry tongue) was present. The conjunctivae were hyperemic and bilateral cervical adenopathy was present. Rales were present in the right base. The cardiac examination revealed a normal S_1 and S_2 without murmurs or extra sounds. The abdomen was soft and nontender with a liver span of 7.5 cm, and the spleen tip was not palpable. The musculoskeletal examination revealed moderate tenderness on movement of the left elbow and hip, with no swelling or increased warmth. The neurologic examination findings were normal.

Admission laboratory values included a hemoglobin level of 0.11 g/L; a hematocrit value of 0.32; a white blood cell (WBC) count of 12.1×10^9/L, with 0.82 segmented neutrophils, 0.05 lymphocytes, and 0.09 eosinophils; a platelet count of 565×10^9/L; and an erythrocyte sedimentation rate of 55 mm/h. Urinalysis revealed 0 to 5 WBCs per high-power field. Blood, urine, and throat cultures obtained on admission were negative. The evaluation included negative serologic reactions for Rocky Mountain spotted fever, rubella, rubeola, monospot, and rapid plasma reagin. Rheumatoid factor, antinuclear antibody, C3, C4, and C1q binding assays were within normal limits. Serum immunoglobulin values were IgG, 17.3 g/L (range, 2.17 to 9.04 g/L); IgA, 3.60 g/L (range, 11 to 90 g/L); IgM, 1.85 g/L (range, 34 to 126 g/L); and IgE, 17 μg/L (0 to 12 μg/L). Aspirin therapy (90 mg/kg/d) was begun for the fever and arthralgias.

On day 9 of hospitalization, periungual desquamation as well as flaky desquamation of the rash developed. The fever resolved by this time, and the dose of aspirin therapy was decreased to 30 mg/kg/d and tolmetin sodium therapy was added for the arthralgias. The platelet count had risen to over 1000×10^9/L. The electrocardiogram and echocardiogram obtained on days 2 and 9, respectively, were normal. The patient was discharged while receiving tolmetin sodium (200 mg three times a day) and aspirin (30 mg/kg/d) on the tenth day of hospitalization. Nine days later, the patient was readmitted with diffuse petechiae and subconjunctival hemorrhages. Admission laboratory values included a hemoglobin level of 0.09 g/L, a hematocrit value of 0.29, and a WBC count of 8.9×10^9/L, with 0.44 segmented neutrophils, 0.36 lymphocytes, and 0.16 eosinophils. The platelet count was 17×10^9/L and the erythrocyte sedimentation rate was 59 mm/h. Prothrombin time, partial thromboplastin time, and urinalysis findings were within normal limits. The bone marrow aspiration revealed a normocellular marrow with an increased number of megakaryocytes. A diagnosis of ITP was made and treatment with prednisone (2 mg/kg/d) was begun. By the third day of therapy, no new petechiae were noted and the platelet count was rising. Direct platelet-associated antibodies were positive with 7 fg of IgG platelet, and indirect platelet antibodies were negative (2 fg of IgG per platelet). A repeated echocardiogram was normal. The prednisone therapy was tapered and then discontinued over the next three months by the local pediatrician with normalization of the platelet count and hematocrit value.

Comment.—Herein we describe a child with Kawasaki disease followed by ITP, which, to our knowledge, has not been previously reported. Kawasaki disease is a multisystem disorder of unknown cause with varying clinical expression and established diagnostic criteria. Although the cause of Kawasaki disease remains uncertain, epidemiologic data suggest that an infectious agent is involved, with apparent seasonal peaks as well as sporadic endemic occurrences.[2,3] In addition, several investigators have demonstrated immunologic abnormalities that may be related to the initiation and/or perpetuation of the inflammatory vasculitis. There is an acute rise and convalescent fall in all immunoglobulin values, which may represent a primary response to the inciting agent or a nonspecific polyclonal activation.[1] Immune complexes have been detected in approximately 50% of patients by C1q or Raji assay.[4] These tend to peak about four weeks after onset and then decline rapidly. Serum complement levels have been studied, and the C3 level is often elevated in the acute phase while the C4 level is normal throughout the disease course.

The combination of circulating immune complexes with normal complement is different from the classical immune complex disorders in which complement is consumed. Levin et al[5] have suggested that immune complexes in Kawasaki disease aggregate platelets and release vasoactive factors from platelet cytosol. They found a platelet aggregating factor in the serum of patients with Kawasaki disease that shares some characteristics of immune complexes. The association of thrombocytosis with the presence of circulating platelet aggregating material is paradoxical. Aggregated or damaged platelets are normally removed rapidly from the circulation by

the reticuloendothelial system (RES), leading to thrombocytopenia rather than thrombocytosis. It has been observed that saturation of the RES delays the clearance of immune complexes.[6] Thrombocytosis may therefore be the result of saturation of the RES by immune complexes, a possibility supported by the direct correlation between platelet count and immune complex titers.[6] The increased platelet aggregation demonstrated in patients with Kawasaki disease may be related to diminished endothelial cell production of prostacyclin.[7] Thus, interactions between immune complexes and platelets may be important in Kawasaki disease.

This child developed ITP during the convalescent stage of Kawasaki disease. He developed the characteristic hematologic changes of Kawasaki disease, with leukocytosis, anemia, and thrombocytosis. However, thrombocytosis was then followed by a marked drop in the platelet count. The diagnosis of ITP was confirmed by classic bone marrow findings and the presence of platelet-associated antibodies determined by a two-step solid-phase radioimmunoassay, an adaptation[8] of the method of Cines and Schreiber. Idiopathic thrombocytopenia purpura typically follows a viral illness, and epidemiological data suggest that an infectious agent may be a cause of Kawasaki disease as well.[2,3]

Although neither aspirin nor tolmetin therapy commonly produces this picture, drug-induced thrombocytopenia remains a possible explanation.[9] The possibility that Kawasaki disease and ITP were *not* related in this child seems unlikely. We speculate that this child had a viral infection that clinically manifested as Kawasaki disease and immune-mediated thrombocytopenia.

That acute ITP is often preceded by a viral illness is well established, but the relationship between infection and the subsequent destruction of platelets is not completely understood. The appearance of thrombocytopenia and bleeding at a time when virus is ordinarily cleared from the circulation argues against direct interaction between virus and platelet as the cause of thrombocytopenia and suggests that platelets are somehow affected by the immune response to the primary infection. Infectious agents may somehow alter platelet structure so as to cause autologous platelets to become antigenic, or alternatively, antibodies formed against an infecting virus may cross react with a surface constituent of platelets.

Immune complexes are known to be capable of binding to the surface Fc (IgG) receptor on platelet membranes. In one study, antibodies in the serum of children with postrubella thrombocytopenia were found to cause platelet aggregation in the presence of rubella antigen, a property that was lacking in the serum of children who experienced rubella without subsequent thrombocytopenia.[10] These clinical and experimental observations suggest that sudden destruction of platelets in patients recuperating from an infection may be the result of formation of antigen-antibody complexes, which have an affinity for sites on the platelet surface (ie, ITP, drug-induced immunologic thrombocytopenia, post-transfusion purpura). We believe our patient experienced such a condition. Clinicians should be aware of the many different hematological manifestations that can occur with Kawasaki disease, and this patient report illustrates the need to add thrombocytopenia to that list.

ROBERT N. LIPNICK, MD
NAOMI L.C. LUBAN, MD
Departments of Pediatrics and Laboratory Medicine
Children's Hospital National Medical Center
George Washington University Medical School
111 Michigan Ave NW
Washington, DC 20010

1. Hicks RV, Melish ME: Kawasaki syndrome. *Pediatr Clin North Am* 1986; 33:1151-1175.
2. Bell DM, Morens DM, Holman RC, et al: Kawasaki syndrome in the United States. *AJDC* 1983; 137:211-214.
3. Shulman ST, Rowley AH: Does Kawasaki disease have a retroviral aetiology? *Lancet* 1986;2: 545-546.
4. Mason WH, Jordan SC, Sakai R, et al: Circulating immune complexes in Kawasaki syndrome. *Pediatr Infect Dis J* 1985;4:48-51.
5. Levin M, Holland PC, Nokes TJ, et al: Platelet immune complex interaction in pathogenesis of Kawasaki disease and childhood polyarteritis. *Br Med J* 1985;290:1456-1460.
6. Haakenstad AO, Mannik M: Saturation of the reticuloendothelial system with soluble immune complexes. *J Immunol* 1974;112:1939-1948.
7. Burns J, Glude MP, Clark SH, et al: Coagulopathy and platelet activation in Kawasaki syndrome: Identification of patients at high risk for development of coronary artery aneurysms. *J Pediatr* 1984;105:206-211.
8. Loomis K, Kickler TS, Sears D, et al: A simplified radioimmunoassay for antibodies causing immune cytopenia. *Am J Clin Pathol* 1985; 83:12-17.
9. *Drug Information 88: American Hospital Formulary Service*. Bethesda, Md, American Society of Hospital Pharmacist, 1988.
10. Myllyla G, Vaheri A, Uesikari T, et al: Interaction between human platelets, viruses, and antibodies in postrubella thrombocytopenic purpura and platelet aggregation by rubella antigen-antibody interaction. *Clin Exp Immunol* 1969;4:323.

Fructose-1,6-diphosphatase Deficiency: A 20-Year Follow-up

Sir:—Fructose - 1,6 - diphosphatase (FDPase, EC 3.1.3.11) deficiency was first described in 1970.[1] More than 40 patients have been described since then,[2-6] and probably more will be diagnosed as the awareness of this disorder increases among clinicians. Most cases were reported in young patients, and although prognosis in these cases seemed favorable, follow-up to adulthood is still lacking.

The diagnosis of FDPase deficiency has usually been established by liver biopsy, since enzyme activity is undetectable in cultured skin fibroblasts and is extremely low in white blood cells of normal subjects.[3]

Herein we present a 20-year follow-up of a patient known to suffer from FDPase deficiency. Enzyme activity in the patient and his family were determined from an intestinal tissue specimen.

Patient Report.—A 22-year-old man, the first child of non-consanguineous parents of Jewish-Vemenite extraction, had normal growth and development until 20 months of age, when an intercurrent infection induced hypoglycemia and lactic acidosis. On admission, results of a physical examination were unremarkable except for moderate hepatomegaly. The metabolic disturbances were easily corrected by intravenous administration of glucose and bicarbonate. The liver size returned to normal within a few days.

During the ensuing years he suffered more than 30 such episodes, which necessitated hospitalization. These episodes were usually precipitated by minor infections. After puberty, the patient became a vegetarian and consumed mainly fruits and vegetables. Nevertheless, the frequency of the hypoglycemic episodes decreased. The few documented attacks were usually induced by excessive consumption of alcoholic beverages.

At this writing, the patient's physical and intellectual performance were in accordance with his age and he was leading a normal life.

Materials and Methods.—A small-intestinal biopsy was performed following an overnight fast. One hour before the procedure, 10 mg of metoclopramide hydrochloride was given orally. A carry capsule was ingested and directed under fluoroscopy toward the duodenojejunal junction. The specimen was stored at −80°C until enzyme determination.

On the day of determination, the tissue was thawed, weighed, and homogenized

with 20 volumes of 150 mmol/L of potassium chloride, 50 mmol/L of TRIS, 5 mmol/L of magnesium chloride, and 2 mmol/L of edetic acid, and 1 mmol/L of dithioeritritol (pH 7.4). The homogenate was centrifuged at 10000 g for ten minutes and FDPase activity was immediately measured. Enzyme activity was measured spectrophotometrically at 30°C after the production of nicotinamide adenine dinucleotide phosphate (reduced form) according to Racker's method.[7] In a final volume of 1 mL, the reaction mixture contained 50 mmol/L of triethanolamine hydrochloride buffer (pH, 7.5), 2 mmol/L of dithioeritritol, 10 mmol/L of magnesium chloride, 0.2 mmol/L of nicotinamide adenine dinucleotide phosphate, 0.3 IU of phosphoglucoisomerase, 0.15 IU of glucose-6-phosphate dehydrogenase, and 1 mmol/L FDPase. The reaction was linear, with 0.1 to 0.2 mg of protein homogenate added for at least five minutes. The homogenate protein content was determined by the method of Lowry et al.[8] (All substrates and enzymes were purchased from Sigma, St Louis.)

Results.—Soon after the patient's first presentation, two liver biopsies were performed. The glycogen content was 9.6 mg/g of tissue (normal, 4 to 6 mg/g) and the activities of glucose-6-phosphatase, phosphorytase, α-1,6-amyloglucosidase, glycogen synthase, and phosphoenolpyruvate carboxykinase were all within the normal range.

When the patient was 14 years old, an oral glycerol load test was performed. During the test, the plasma glucose concentration was not altered. Oral fructose loading resulted in a drop in the plasma glucose level to 1.5 mmol/L at 60 minutes.

When the patient was 18 years old, hypoglycemia was evident only after 19 hours of controlled fasting. At that time, the lactate level was 4.7 mmol/L (normal, <2.4 mmol/L) and the total serum ketone level was within the normal range (1.7 mmol/L).

The FDPase activity was measured in intestinal biopsy specimens from the proband and his family (Table). The enzyme activity in the patient was 5% to 10% that in controls. The activities in the obligate heterozygotes were below the lower range in the controls. The brother was very likely a heterozygote as well.

Comment.—Our patient suffered from episodes of hypoglycemia and lactic acidosis since early childhood. Low FDPase activity was demonstrated in small-intestinal tissue. At present, FDPase deficiency is a well-established cause of congenital hypoglycemia and lactic acidosis. Unlike the other known enzymatic defects in gluconeogenesis (glucose-6-phosphatase deficiency, pyruvate carboxylase deficiency, or phosphoenolpyruvate carboxykinase deficiency), FDPase deficiency is believed to have a more benign course and a favorable prognosis.[3] The intact glycogen degradation pathway present in FDPase deficiency serves to explain the milder symptoms compared with glucose-6-phosphatase deficiency.

Patients suffering from deficient activity of pyruvate carboxylase have an increased morbidity and mortality, deriving from the ultimate necessity for the reaction product, oxaloacetate, in the citric acid cycle.

Phosphoenolpyruvate carboxykinase deficiency may have symptoms as severe as those of FDPase deficiency, since it does not interfere with glycogen degradation and its product is not necessary for any other cycle. Unfortunately, very few cases have been reported, excluding a reliable comparison between these disorders.

The patient described herein confirms the benign nature of FDPase deficiency and has been leading a normal life since 22 years of age.

The decreasing frequency of episodes seen with advancing age, combined with the prolonged fasting required to induce hypoglycemia, reflect the acquired increased tolerance toward the metabolic consequences of the deficient enzyme, as suggested by Gitzelman et al.[3] This phenomenon is frequently reported in glycogen-storage disease type I and type III. A decreasing frequency of intercurrent infections and an increase in hepatic glycogen content might be the mechanism of this tolerance.

In most case reports,[3] the diagnosis of FDPase deficiency was established in liver biopsy specimens. The lack of activity in cultured skin fibroblasts, the low activity in white blood cells from normal subjects, and the patient's refusal to undergo a third liver biopsy directed us to perform an intestinal biopsy.

Greene et al[9] have diagnosed FDPase deficiency in liver and small-intestinal biopsy specimens. The FDPase determination has been shown to be equally reliable in both kinds of tissue. In our experience, as well as in others', intestinal biopsies have been easier to conduct and, more importantly, much safer than liver biopsies.

Recently, the application of a new radiochemical technique for the determination of FDPase activity in leukocytes was reported.[2] This technique is probably inferior to previously used ones because, in contrast to the values measured in liver or intestinal tissue, the determination in leukocytes cannot differentiate all carriers from controls.

The detection of glycerol-3-phosphate by organic acid chromatography of a patient's urine[6] offers a new method for the diagnosis of FDPase deficiency. However, this metabolite has been detected in small amounts, and only when the patient was hypoglycemic. Therefore, enzymatic studies are still preferred for confirmation of this diagnosis.

Fructose-1,6-diphosphatase Activity in Intestinal Biopsy of the Proband and His Family

Subject	Enzyme Activity*
Proband	1.5/2.2
Father	11.7
Mother	5.9
Brother	7.2
Controls (n = 4)	12.2-20.2

*Enzyme activity is expressed as nanomoles of nicotinamide adenine dinucleotide phosphate produced per minute per milligram of homogenate protein. Two measurements were made in the proband's sample.

ORLY N. ELPELEG, MD
HAGGIT HURVITZ, MD
DAVID BRANSKI, MD
Department of Pediatrics
Bikur-Cholim Hospital
5 Strauss St
Jerusalem, Israel
VARDA BARASH, PHD
Laboratory for Clinical Biochemistry
Hadassah Hospital
Jerusalem, Israel

1. Baker L, Wingrad AI: Fasting hypoglycemia and metabolic acidosis associated with deficiency of hepatic fructose-1,6-diphosphatase activity. *Lancet* 1970;2:13-16.

2. Alexander D, Assaf M, Khundr A, et al: Fructose-1,6-diphosphatase deficiency: Diagnosis using leukocytes and detection of heterozygotes with radiochemical and spectrophotometric methods. *J Inher Metab Dis* 1985;8:174-177.

3. Gitzelman R, Steinman B, Berghe GVD: Essential fructosuria, hereditary fructose intolerance and fructose-1,6-diphosphatase deficiency, in Stanbury JB, Wyngaarden JB, Fredrickson DS, et al (eds): *The Metabolic Basis of Inherited Disease*. New York, McGraw-Hill International Book Co, 1983, ed 5, pp 118-140.

4. Hommes FA, Campbell R, Steinart C, et al: Biochemical observation on a case of hepatic fructose-1,6-diphosphatase deficiency. *J Inherited Metab Dis* 1985;8:169-173.

5. Kinugasa A, Furukawa N, Kodo N, et al: Ten years follow-up study on a patient with fructose-1,6-diphosphatase deficiency. Read before the Fourth International Congress of Inborn Errors of Metabolism, Sendai, Japan, May 23-27, 1985.

6. Krywawych S, Katz G, Lawson AM, et al: Glycerol-3-phosphate excretion in fructose-1,6-diphosphatase deficiency. *J Inherited Metab Dis* 1986;9:388-392.
7. Racker E: Fructose-1,6-diphosphate from spinach leaves, in Colomick SP, Kaplan NO (eds): *Methods in Enzymology.* New York, Academic Press Inc, 1962, vol 5, pp 272-276.
8. Lowry OH, Rosebrough NJ, Farr AL, et al: Protein measurement with the folin phenol reagent. *J Biol Chem* 1951;193:265-275.
9. Greene HL, Stifel FB, Herman RH: 'Ketotic hypoglycemia' due to hepatic fructose-1,6-diphosphatase deficiency. *AJDC* 1972;124:415-418.

Pyloric Stenosis in Sick Premature Infants

Sir:—We noted with dismay that Tack et al[1] failed to appreciate that pyloric stenosis in a sick premature infant is readily diagnosed by palpating a pyloric tumor. If the diagnosis is suspected, recourse to radiologic investigation is unnecessary. The key to the diagnosis of pyloric stenosis in the sick premature infant is the knowledge that it can occur and can be diagnosed accurately clinically. Indeed, in our experience, palpation of the pyloric tumor is somewhat easier in the sick premature infant than in the otherwise well older infant. Furthermore, careful observation of the upper abdomen reveals conspicuous gastric peristalsis.

It seems a sad trend that the diagnosis of such a simple pediatric condition is not being made clinically. We hope that the art of clinical examination is not being lost in high-tech units, where it seems to be easier to resort to radiologic investigation.

Spencer W. Beasley, FRACS
John M. Hutson, MD, FRACS
Division of Pediatric Surgery
Royal Children's Hospital
Flemington Road
Parkville, Victoria 3052
Australia

1. Tack ED, Perlman JM, Bower RJ, et al: Pyloric stenosis in the sick premature infant: Clinical and radiological findings. *AJDC* 1988; 142:68-70.

In Reply.—The objective of our report was to highlight what, in our experience, is not a simple pediatric condition to diagnose clinically in the sick premature infant. None of the infants described in our report had clinical evidence of a pyloric tumor or "conspicuous gastric peristalsis." This is not surprising, since atony of the stomach with prominent gastric dilatation is the most frequent finding in our experience when an upper-gastrointestinal-tract study is performed in a sick premature infant suspected of having a gastric outlet obstruction. Despite our "high-tech" environment, we also take pride in our clinical skills. However, we caution against an infallible belief that in the critically ill premature infant, the presence of a pyloric tumor or visible peristalsis waves can always be found. Our point in presenting the cases was to emphasize the importance of considering this diagnosis even in an unlikely patient population.

Jeffrey M. Perlman, MD
Division of Newborn Medicine
Richard J. Bower, MD
Division of Pediatric Surgery
Edward Mallinckrodt Department of Pediatrics
Children's Hospital at Washington University Medical Center
400 S Kingshighway
St Louis, MO 63110

DICE: Nonclinical Causes of Overtreatment

Sir:—A vague clinical concept led to the medical odyssey described by Dr Stickler in the September 1988 issue of *AJDC*.[1] However, when there is overtreatment, professional competition and overspecialization are frequent synergists. The acronym "DICE," which is described below, helps explain the pathogenesis of overtreatment.

Diffused responsibility.—Each physician's sense of responsibility for therapeutic catastrophe declines in proportion to the number of consultants on a case. This is true all along the pecking order, from the primary physician who first asks for help to the surgeon who promises to cure.

Inexperience.—Clinicians tolerate wider deviations from normal as their experience increases. Clinicians with the least experience are most likely to be anxious about the need for treatment. An important element of inexperience is lack of familiarity with the child and the family.

Cookbook thinking. — Children whose growth is more than 2 SDs below the mean are abnormal. Abnormalities require evaluations. Evaluations reveal other abnormalities. All abnormalities are summed to arrive at a single disease. Diseases must be treated. In Dr Stickler's report, a growth chart plus an esophageal probe was the recipe for overtreatment.

Economics.—Professional income and status still depend on treatments, procedures, and hospital admissions. This is true even in a salaried group practice where income and status are shared. These incentives alter the clinical perception of what is abnormal and lend additional momentum to the impulse toward treatment.

Since the boundary between normal and abnormal is usually vague, we will always have to reckon with elastic concepts like "failure to thrive" and "short stature." DICE will help alert us to the nonclinical factors that overstretch such concepts and lead to overtreatment.

Allan S. Cunningham, MD
Department of Pediatrics
The Mary Imogene Bassett Hospital
Cooperstown, NY 13326-1394

1. Stickler GB: Gastrostomy dependence in two constitutionally short children. *AJDC* 1988;142:937-939.

Hidden Salicylates

Sir:—The media has educated the general public about the potential danger of Reye's syndrome with the use of aspirin, especially during influenza or chickenpox. What the media has not warned the public about is that an over-the-counter product may not list aspirin as an ingredient, but it may have salicylates in a combined form. The case in point is Pepto-Bismol, a common over-the-counter item found in many home medicine cabinets. This pleasant-tasting product is commonly used for upset stomach, nausea, and diarrhea. Many family practice physicians and pediatricians prescribe this medication for adults as well as children. In fact, children as young as 3 years old may take this medication. The problem lies in the fact that bismuth subsalicylate is the main ingredient in Pepto-Bismol and yields 130 mg of salicylate per tablespoon. The dosage for children ranges from 1 to 3 teaspoonfuls for up to eight doses a day. This means that the salicylate content could range from 120 to 340 mg/d, a real potential to cause Reye's syndrome in children.

I believe that primary care physicians, pediatricians, pharmacists, and other medical professionals should be aware of such "hidden salicylates" for their patients, especially when influenzalike symptoms are present.

Prof Michael D. Szap
Arnold and Marie Schwartz College of Pharmacy
Long Island University
DeKalb Ave and Flatbush Ext
Brooklyn, NY 11220

Serious medicine for head and chest congestion

Triaminic® Expectorant is the congestion medicine for colds and allergies.

It clears congestion. In the head. And in the chest. Because it contains both a decongestant and an expectorant.

The decongestant shrinks swollen nasal and sinus membranes. Relieves the pressure. Promotes nasal drainage.

The expectorant loosens phlegm and clears bronchial passageways.

Triaminic Expectorant. No wonder it's the pediatrician's choice for head and chest congestion.

#1 PEDIATRICIAN RECOMMENDED

Triaminic®
EXPECTORANT

The congestion medicine

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

Bicillin® C-R 900/300

(penicillin G benzathine and penicillin G procaine suspension)

Because compliance doesn't have t
depend on who's tending the tots.

WYETH-AYERST LABORATORIES™

©1987, Wyeth-Ayerst Laboratories

Philadelphia, PA 19101

Human Plague—United States, 1988

AS OF SEPTEMBER 1, 14 nonfatal cases of human plague had been reported in the United States during 1988. Ten cases were in males, and patients' ages ranged from 8 to 82 years. Each resulted from exposure to sources of wild rodent plague in the western United States: four cases were acquired in Colorado, six in New Mexico, two in California, and one each in Arizona and Texas.

Some of the cases presented interesting epidemiologic and/or clinical features:

Case 3. Illness in a 12-year-old Zuni Indian boy was diagnosed promptly as plague and treated with oral tetracycline and intravenous gentamicin. He appeared to recover until the sixth day after onset, when he had headaches and recurrence of fever. Physical examination revealed spinal rigidity, and plague meningitis was diagnosed. The boy then was given chloramphenicol and has recovered.

Case 7. A 19-year-old male Army recruit had received 0.1 mL Plague Vaccine, U.S.P. (Cutter Biological) intramuscularly (IM) in August 1987 and a 0.2 mL booster dose IM in November 1987. On July 14, 1988, he had onset of illness and was hospitalized with fever, malaise, an inguinal bubo, and multiple insect bites on both legs. He was treated with tetracycline and chloramphenicol and recovered. Exposure to infection probably occurred during military training maneuvers at Fort Hunter Liggett in Monterey County, California. This area is a plague focus that principally involves California ground squirrels (Spermophilus beecheyi) and their fleas. During a field investigation in the maneuver area, an intensive localized epizootic was detected and Yersinia pestis isolated from fleas.

CDC Editorial Note: More than 90% of human plague infections occur in the southwestern United States—particularly in New Mexico, Arizona, California, and Colorado (1; CDC, unpublished data). However, plague may occur in residents of or visitors to areas of other western states.

Typically, more than half of human plague cases occur in males (137 (57%) of the 239 cases from 1975 to 1987), and approximately half occur in persons less than 20 years old (1; CDC, unpublished data).

From 1975 through 1987, 30% of all human plague cases were in Native Americans.[2]

Plague Vaccine, U.S.P., is commercially available from Cutter Biological in Berkeley, California, and is recommended for persons repeatedly exposed to possible plague infection (laboratory personnel or persons with frequent and regular contact with rodents in plague-infected areas).

HIV-Related Beliefs, Knowledge, and Behaviors Among High School Students

IN 1987, CDC began to assist state and local departments of education in assessing human immunodeficiency virus (HIV)-related beliefs, knowledge, and behaviors among high school students in states and cities with the highest cumulative incidence of acquired immunodeficiency syndrome (AIDS).[1,2] Departments of education will use the results of these surveys to plan school HIV education programs and to monitor temporal changes in HIV-related beliefs, knowledge, and behaviors among high school students. This report presents selected baseline data from surveys conducted during the spring of 1988.

A questionnaire for anonymous self-administration was developed collaboratively by representatives of 24 state and local departments of education, with technical assistance from CDC. The questionnaire contained 49 core questions: four to assess demographic characteristics of respondents, 33 to assess HIV-related beliefs and knowledge, and 12 to assess behaviors associated with HIV transmission. Each department of education that conducted the survey first completed the appropriate state or local survey review and approval process.

The survey included samples of students in grades 9-12 (ages 13-18 years) in each of six cities (Chicago, Los Angeles, New Orleans, New York City, San Francisco, and Seattle) and in each of nine states (California, District of Columbia*, Kentucky, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Washington). Samples from California, New York, and Washington excluded students in Los Angeles, San Francisco, New York City, and Seattle; data from these four cities were collected and analyzed separately. Each site chose which of the 49 questions to administer; nearly every site obtained information using all the questions regarding demographic characteristics and HIV-related beliefs and knowledge. Four sites (California, District of Columbia, Michigan, and San Francisco) used the 12

questions to assess the extent to which students engage in behaviors that may result in HIV infection.

Almost all respondents believed students their age should be taught about AIDS** in school (range, 89.0% to 96.8%). Knowledge about sources for correct information about AIDS varied greatly among sites (range, 41.1% to 70.5%).

The range of students who knew that AIDS is not transmitted through shaking hands was 85.5% to 95.6%; through giving blood, 27.8% to 53.3%; from mosquito or other insect bites, 28.9% to 46.8%; from using public toilets, 41.8% to 64.6%; and from having a blood test, 49.6% to 75.4%. A range of 83.8% to 98.4% of students knew that AIDS is transmitted by sharing needles or syringes used to inject drugs; 88.3% to 98.1% knew that AIDS is transmitted through sexual intercourse.

High school students from four sites reported variable rates of intravenous (IV)-drug use and sexual intercourse: 2.8% to 6.3% reported ever injecting cocaine, heroin, or other illegal drugs; 28.6% to 76.4% reported having had sexual intercourse at least once. At each site, more male than female students and more older than younger students reported ever injecting illegal drugs or ever having had sexual intercourse.

The percentage of students who reported having had three or more sex partners ranged from 15.1% to 42.6%. At each site, more male than female students (range for males, 24.2% to 67.3%; for females, 8.3% to 25.6%) and more older than younger students reported three or more sex partners (range for 13- and 14-year-olds, 7.5% to 45.5%; for 15- and 16-year-olds, 13.0% to 39.4%; and for 17- and 18-year-olds, 29.9% to 47.7%).

CDC Editorial Note: In the fall of 1987, CDC began providing fiscal and technical assistance to 15 state and 12 local departments of education that serve areas with the highest cumulative incidence of AIDS. The purpose of this assistance was to help schools implement effective HIV education programs.

Baseline data reported here suggest that HIV-related beliefs, knowledge, and behaviors among the adolescents surveyed in 15 states and cities are generally similar. Many students incorrectly thought that HIV infection may be acquired from giving blood, using public toilets, or having a blood test or from mosquito and other insect bites. Most students knew sexual intercourse and IV-drug use can result in HIV infection. Students who reported using IV drugs or having sexual intercourse, particularly with multiple partners, are at risk for HIV infection. Departments of education should implement programs to correct misperceptions about HIV transmission, to reduce behaviors resulting in HIV infection, and to assess periodically whether these misperceptions and behaviors change among high school students over time.[3]

References

1. Kolbe L, Jones J, Nelson G, et al. School health education to prevent the spread of AIDS: overview of a national program. Hygie 1988;7(3):10-3.
2. Kann L, Nelson GD, Jones JT, Kolbe L. Establishing a system of complementary school-based surveys to periodically assess AIDS-related knowledge, beliefs, and behaviors among adolescents. J Sch Health 1989 (in press).
3. CDC. Guidelines for effective school health education to prevent the spread of AIDS. MMWR 1988;37(suppl S-2).

*District of Columbia is categorized as a state for funding purposes.

**When the questionnaire was developed in 1987, representatives of state and local departments of education believed students would not understand the term "HIV infection"; thus, the term "AIDS" was used.

Update: Influenza Activity—Worldwide—and Influenza Vaccine Availability—United States

UPDATE

IN 1988, influenza-like illness worldwide has been associated with all three virus types—A(H3N2), A(H1N1) and B.

Oceania. In New Zealand, activity began in April and peaked in June. Virus isolates have been almost exclusively type A(H3N2). Persons of all ages have been infected, and one influenza-associated death has been confirmed. In Australia, type A(H1N1) virus predominated; in western Australia, type A(H3N2) virus has also been isolated.

Asia. In June, outbreaks of influenza A(H1N1) occurred among schoolchildren in southern China. In addition, Hong Kong and Singapore reported sporadic cases. The Republic of Korea has reported only sporadic cases since April. Taiwan, where type B virus was reported early in the year, reported localized outbreaks of type A(H1N1) virus in June and July.

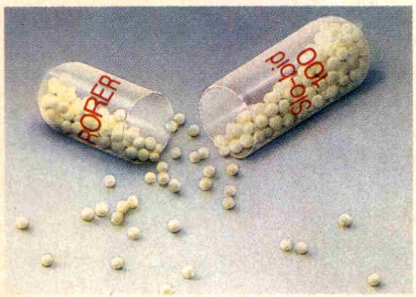
South America. Chile and Uruguay have reported widespread influenza A(H3N2) activity. Type B noted in Uruguay and Argentina.

Europe and United States. Influenza has been isolated in Europe and the United States throughout the summer. Czechoslovakia reported type A(H1N1) virus activity. In the United States, influenza B isolates were reported from Arizona during June, July, and August and from Texas in late July. Type A(H1N1) virus was isolated from a child with non-Hodgkin's lymphoma in Washington, D.C., in late July.

INFLUENZA VACCINE AVAILABILITY—UNITED STATES

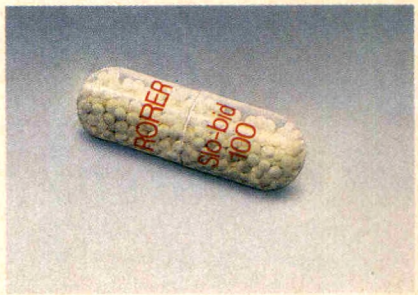
Production of the trivalent influenza vaccine for the 1988-89 season has been delayed, resulting in a 4-6-week delay in vaccine distribution for some areas. Health-care providers and public health departments should ensure that priority is given to targeting vaccination activities toward persons at high risk for influenza-associated complications.

Growing up on a steady theophylline is an open-and-shut case



Sprinkled

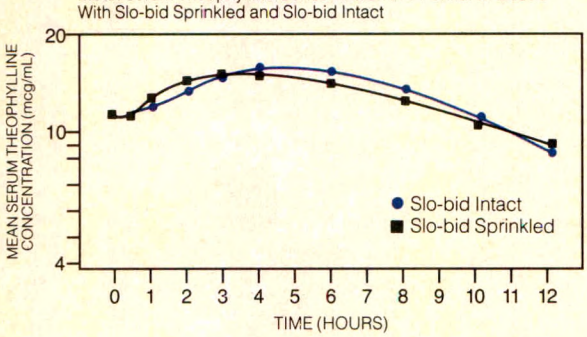
Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration[1]

Mean Serum Theophylline Concentration in 14 Children Dosed With Slo-bid Sprinkled and Slo-bid Intact



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.[2]

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in applesauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

In asthma and bronchitis

Slo-bid™ 12

(theophylline, anhydrous)

Nothing beats our system

From the makers of Azmacort™ (triamcinolone acetonide)

Please see next page for brief summary of prescribing information.

©1989 Rorer Pharmaceutical Corporation
Printed in U.S.A. FC#89-40 SB06189A 1/89

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA. U.S.A. 19034

Slo-bid™

(theophylline, anhydrous)
50 mg, 100 mg, 200 mg, and 300 mg

Gyrocaps®
Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 100 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 μg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 μg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 μg/mL.

Information for Patients:
The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:
Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Rifampin	Decreased serum theophylline levels

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromotography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C – Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness of Slo-bid Gyrocaps administered:
1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

50 mg – Clear (cap) and opaque white (body) capsule with 50 printed in red
100 mg – Clear capsule with 100 printed in red
200 mg – Opaque white (cap) and clear (body) capsule with 200 printed in red
300 mg – Opaque white capsule with 300 printed in red

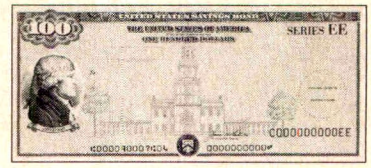
Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0057-99) and in unit dose 10 x 10 (NDC 0075-0057-62). Slo-bid Gyrocaps 100 mg are available in bottles of 100 (NDC 0075-0100-00), bottles of 1000 (NDC 0075-0100-99) and in unit dose 10 x 10 (NDC 0075-0100-62). Slo-bid Gyrocaps 200 mg are available in bottles of 100 (NDC 0075-0200-00), bottles of 1000 (NDC 0075-0200-99) and in unit dose 10 x 10 (NDC 0075-0200-62), and Slo-bid Gyrocaps 300 mg are available in bottles of 100 (NDC 0075-0300-00), bottles of 1000 (NDC 0075-0300-99) and in unit dose 10 x 10 (NDC 0075-0300-62), and are manufactured by:

RORER PHARMACEUTICALS
a division of
Rorer Pharmaceutical Corporation
Fort Washington, PA, U.S.A. 19034

ROER

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

Portrait of the Great American Investor



You wouldn't know it to look at him. But he has an investment plan that's working, even though he's not.

From Elm Street to Wall Street, people all over America are discovering that U.S. Savings Bonds have changed.

When held for five years or more, Bonds pay competitive rates, like money market accounts. They're also free from state and local income tax. Find out more, call anytime 1-800-US-BONDS.

Bonds held less than five years earn a lower rate.

A public service of this publication.

U.S. SAVINGS BONDS
THE GREAT AMERICAN INVESTMENT

The Editorial Board Speaks . . .

Henry L. Nadler, MD

Henry has been a leading light in genetics, metabolic disorders, and general pediatric issues. His career is a distinguished one, as described previously in this feature (*AJDC* 1987;141:138). In the last year, he has added to his many distinctions by receiving the Meyer O. Cantor Award for Distinguished Service to International Medicine and Humanity from the American College of Surgeons (1987). In 1988, he moved from the deanship of Wayne State University School of Medicine, which he had held since 1981, to his present post as president of Michael Reese Hospital and Medical Center in Chicago, where he also is professor of pediatrics. Despite his administrative duties, he remains an active contributor to genetics and pediatrics as witnessed by his more than 225 publications, including the recent release of *Prenatal Diagnosis and Therapy* published by Churchill Livingston Inc in 1988 and coauthored by J. Charrow and M. I. Evans. Henry has been a valuable *AJDC* Editorial Board member and remains an avid, low-scoring golfer.

FETAL TISSUE TRANSPLANTATION

The subject of human fetal tissue transplantation has recently become the focus of major public policy debate. In March 1988, Dr Robert Windom, Assistant Secretary of Health, clearly focused the issue for the biomedical community by prohibiting the National Institutes of Health, Bethesda, Md, from conducting intramural research on the transplantation of fetal tissue pending the recommendation of a special advisory committee.

Fetal tissue has long been utilized for biomedical research. The development of the polio vaccine in the 1950s could not have been accomplished without the ability to utilize human fetal kidney cells. Whole fetal thymus transplantation for the treatment of DiGeorge's syndrome resulted in few ethical discussions. In contrast, the recent attempts at treatment of Parkinson's disease, Alzheimer's disease, and diabetes, with fetal tissue transplants, have raised numerous ethical, moral, and legal questions.

It is interesting to speculate why the issue of fetal tissue transplantation has evoked so much discussion. In my opinion, the answer relates to the societal debate surrounding the morality and legality of abortion. As a biomedical and social community we have become comfortable with the general issue of organ transplantation as practiced today. We have developed stringent guidelines to protect donors and established criteria for determining death. Questions relating to concepts of morbidity and death and use of live fetuses have been widely discussed.

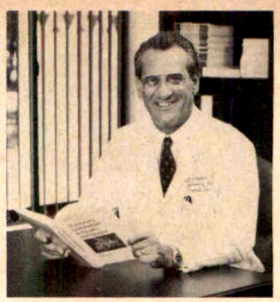
The Human Fetal Tissue Transplantation Research Panel was asked to respond to the following specific questions put forward by the Secretary of Health:

1. Is an induced abortion of moral relevance to the decision to use human fetal tissue for research? Would the answer to this question provide any insight as to whether and how this research should proceed?
2. Does the use of the fetal tissue in research encourage women to have an abortion that they might otherwise not undertake? If so, are there ways to minimize such encouragement?
3. What actual steps are involved in procuring the tissue from the source to the researchers? Are there any payments involved? What types of payments in this situation, if any, would fall inside or outside the scope of the Hyde Amendment?
4. According to the Department of Health and Human Services regulations, research on dead fetuses must be conducted in compliance with state and local laws. A few states' enacted version of the Uniform Anatomical Gift Act contains restrictions on the research applications of dead fetal tissue after an induced abortion. In those states, do these restrictions apply to therapeutic transplantation of dead fetal tissue after an induced abortion? If so, what are the consequences for National Institutes of Health–funded researchers in those states?
5. For those diseases for which transplantation using fetal tissue has been proposed, have enough animal studies been performed to justify proceeding to human transplants? Because induced abortions during the first trimester are less risky to the woman, have there been enough animal studies for each of those diseases to justify the reliance on the equivalent of the second-trimester human fetus?
6. As a legal matter, does the very process of obtaining informed consent from the pregnant woman constitute a prohibited "inducement" to terminate the pregnancy for the purposes of the research—thus precluding research of this sort, under the Department of Health and Human Services regulations?
7. Is maternal consent a sufficient condition for the use of the tissue, or should additional consent be obtained? If so, what should be the substance and who should be the source(s) of the consent, and what procedures should be implemented to obtain it?
8. Should there be and could there be a prohibition on the donation of fetal tissue between family members, or friends and acquaintances?
9. Would a prohibition on donation between family members jeopardize the likelihood of clinical success?
10. If transplantation using fetal tissue from induced abortions becomes more common, what impact is likely to occur on activities and procedures employed by abortion clinics? In particular, is the optimal or safest way to perform an abortion likely to be in conflict with preservation of the fetal tissue? Is there any way to ensure that induced abortions are not intentionally delayed to have a second-trimester fetus for research and transplantation?
11. What is the likelihood that transplantation using fetal cell cultures will be successful? Will this obviate the need for fresh fetal tissue? In what time frame might this occur?

Each pediatrician should carefully consider these questions. We have a responsibility to be knowledgeable about the issue and respond appropriately. Even though the committee recently agreed that it is morally acceptable to use human fetal tissue obtained from legal abortions for research and therapy, the debate is certainly not over. Fetal transplantation holds great promise as an effective therapeutic modality for the treatment of many significant diseases. Knowledge gained from evaluation of fetal tissue will be critical to understanding not only diseases but also normal growth and development.

"Everything comes to a stop in my office until I've read A PIECE OF MY MIND in each new issue of JAMA."

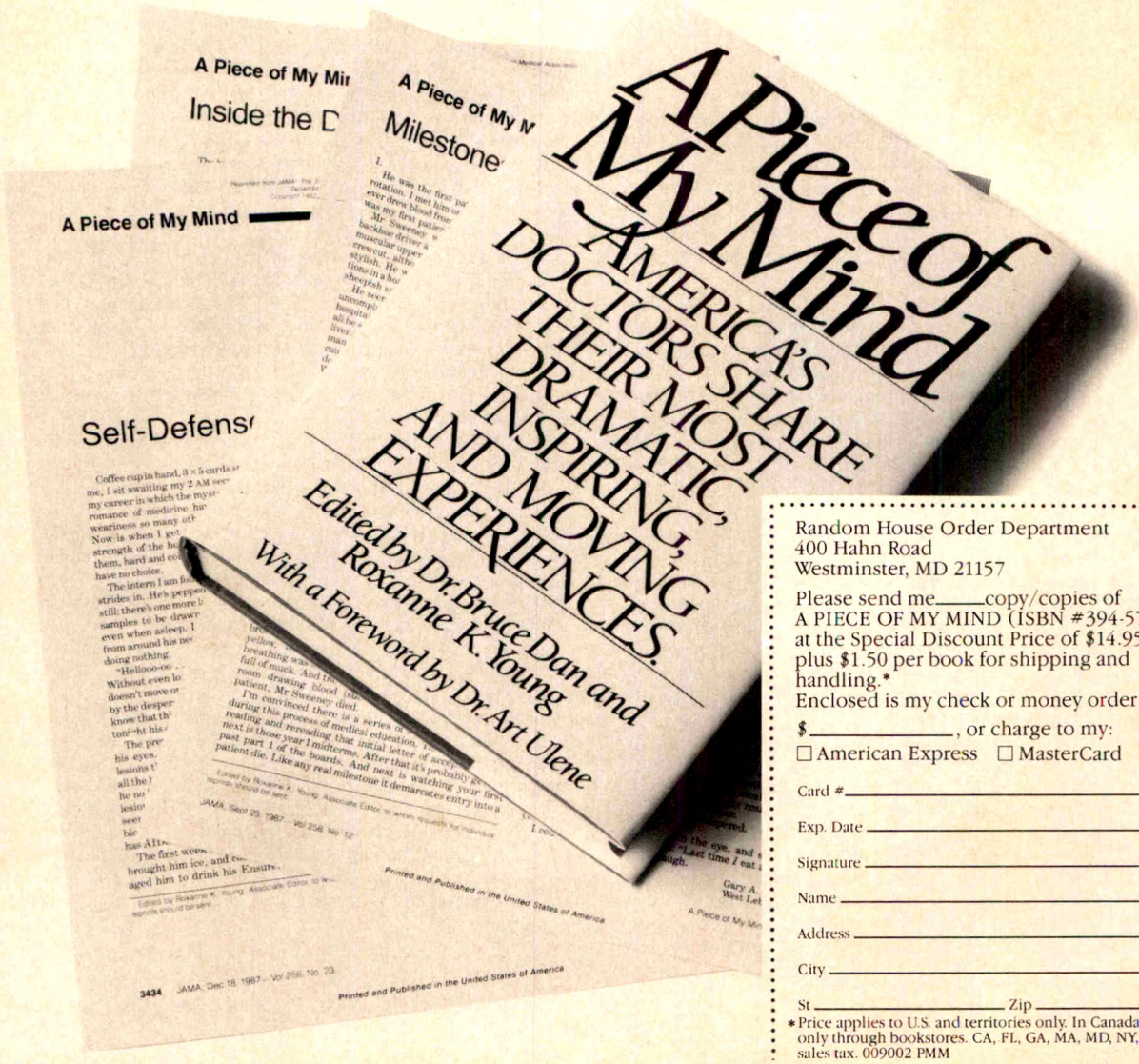
W. G. Scoggins, MD



Now it's a book

The column you've loved for years is now collected in a handsomely bound hardcover book. Eighty extraordinary pieces, the best of the immensely popular A PIECE OF MY MIND columns from JAMA, are brought together for the first time. Relive the joys and sorrows of practicing medicine. Share the stories with your friends and loved ones.

Special Discount Physicians receive a $4.00 discount off the $18.95 cover price. You pay only $14.95 per copy plus shipping and handling. Call this toll-free number today, 1/800-638-6460 (in Maryland, 1/800-492-0782) Credit cards only. Or, if you prefer, send the coupon with your check. Allow 4 weeks for delivery.



Random House Order Department
400 Hahn Road
Westminster, MD 21157

Please send me____copy/copies of A PIECE OF MY MIND (ISBN #394-57715-9) at the Special Discount Price of $14.95 each plus $1.50 per book for shipping and handling.*
Enclosed is my check or money order for
$_____, or charge to my:
☐ American Express ☐ MasterCard ☐ Visa

Card #_____

Exp. Date _____

Signature _____

Name _____

Address _____

City _____

St _____ Zip _____

*Price applies to U.S. and territories only. In Canada available only through bookstores. CA, FL, GA, MA, MD, NY, TN, add sales tax. 009002 PMM

Who has time for allergies when you are performing emergency surgery

Kids can't operate when allergy symptoms get in their way. Tavist® Syrup (clemastine fumarate) 0.67mg/5ml, helps kids by effectively relieving symptoms of allergic rhinitis and mild urticaria.

With a pleasant citrus flavor and convenient b.i.d. dosage, Tavist® Syrup provides up to 12 hours of relief.

Prescribe Tavist® Syrup. So kids can perform to their full potential.

Tavist® Syrup. Lets kids be kids 12 hours long

(clemastine fumarate) 0.67mg/5ml

© 1989 Sandoz Pharmaceuticals Corporation

Please see a brief summary of prescribing information on the following page.

TAS-189-1

BRIEF SUMMARY

TAVIST®

(clemastine fumarate) SYRUP 0.5 mg/5 ml
(present as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

Tavist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see *DOSAGE AND ADMINISTRATION*).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see *PRECAUTIONS — Drug Interactions* in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see *PRECAUTIONS — Nursing Mothers* in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist® (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (6 mg clemastine).

For Urticaria and Angioedema — The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

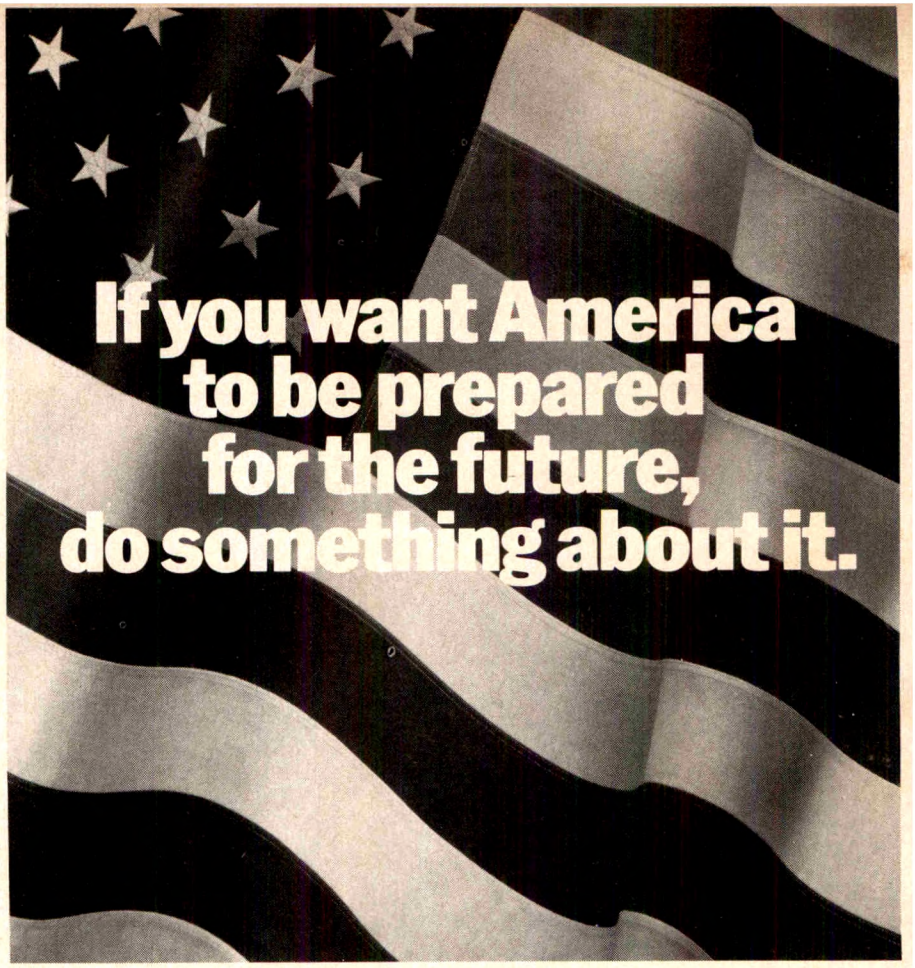
HOW SUPPLIED

Tavist® (clemastine fumarate) Syrup

Clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

[TAS-Z3 APRIL 1, 1986]

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500



Support America's colleges. Because college is more than a place where young people are preparing for their future. It's where *America* is preparing for *its* future.

If our country's going to get smarter, stronger—and more competitive—our colleges and universities simply must become a national priority.

It's an investment we all share in. Government. Private citizens. And the business community. After all, the future of American business depends on it.

So help America prepare for the future with a corporate gift to the college of your choice—and you'll know your company has done its part.

Give to the college of your choice.

Ad Council A Public Service of This Publication

COUNCIL FOR AID TO EDUCATION CFAE

Failure of Once-Daily Penicillin V Therapy for Streptococcal Pharyngitis

Michael A. Gerber, MD; Martin F. Randolph, MD; Kathleen DeMeo; Henry M. Feder, Jr, MD; Edward L. Kaplan, MD

• To determine if a single daily dose of penicillin V would be effective in the treatment of group A β-hemolytic streptococcal (GABHS) pharyngitis, 154 patients with GABHS pharyngitis were randomly assigned to receive 750 mg of penicillin V once daily for ten days or 250 mg of penicillin V three times daily for ten days. The two regimens were comparable in their ability to eradicate GABHS from the upper respiratory tract in 18 to 24 hours and in their impact on the clinical course of the disease. However, a bacteriologic treatment failure occurred in six (8%) of the 76 patients in the three-times-daily group and in 16 (22%) of the 74 patients in the once-daily group. These findings support the current recommendation that penicillin V be given in two or more divided doses for a full ten days for the treatment of GABHS pharyngitis.

(*AJDC* 1989;143:153-155)

An orally administered antibiotic regimen for the treatment of group A β-hemolytic streptococcal (GABHS) pharyngitis that could be given once rather than several times each day would be convenient, especially for children who are attending school, for single-parent families, and for families in which both parents work. A single daily dose might also result in improved patient compliance.

In an earlier investigation[1] we demonstrated that a 30-mg/kg dose of cefadroxil monohydrate given once daily for ten days was as effective in the treatment of GABHS pharyngitis as a 250-mg dose of penicillin V potassium given three times daily for ten days. These two antibiotic regimens were comparable in their ability to eradicate GABHS from the upper respiratory tract, in their impact on the clinical course of the disease, and in their bacteriologic treatment failure rate. Although rheumatic fever prevention was not specifically examined in the earlier study, the fact that eradication of GABHS from the upper respiratory tract is the sine qua non for the prevention of rheumatic fever[2] suggests that these two antibiotic regimens would be comparable in their ability to prevent this nonsuppurative sequela of GABHS pharyngitis. In addition, compliance was substantially better in the cefadroxil-treated than in the penicillin-treated patients.

The effectiveness of a 30-mg/kg dose of cefadroxil given once daily for ten days in the treatment of GABHS pharyngitis has been corroborated by other investigators,[3] and this regimen has recently received Food and Drug Administration approval. However, a major drawback to the use of once-daily cefadroxil is its tremendous expense relative to that of penicillin.[4] Although the only previously reported attempt to treat GABHS pharyngitis with a single daily dose of oral penicillin was unsuccessful, Breese et al[5] used penicillin G and evidence suggests that penicillin V may be a more effective agent.[6] Therefore, we initiated a prospective, randomized, controlled investigation to compare the effectiveness of two treatment regimens for GABHS pharyngitis: 750 mg of penicillin V given orally once daily, and the conventional regimen of 250 mg of penicillin V given orally three times daily. Outcome was measured by the ability to isolate GABHS from the upper respiratory tract 18 to 24 hours after the beginning of therapy, the impact on the clinical course, and the bacteriologic treatment failure rate.

PATIENTS AND METHODS

During the winter-spring of 1985-1986, 225 consecutive patients seen in a private pediatric office in Danbury, Conn (M.F.R.), with clinical findings suggestive of GABHS pharyngitis were enrolled in the investigation after written informed consent had been obtained. Patients with a history of hypersensitivity to penicillin and patients who had received antibiotic therapy within the previous 72 hours were excluded.

All study patients were evaluated as previously described[7] for the presence and severity of two objective signs (fever and cervical lymphadenitis as manifested by tender, enlarged lymph nodes) and three subjective symptoms (sore throat, headache, abdominal pain) before and 18 to 24 hours after the initiation of antibiotic therapy. A throat culture was obtained from each patient by vigorously swabbing the posterior pharynx and tonsils (or tonsillar fossae) with a rayon-tipped swab (Culturette, Marion Scientific, Kansas City, Mo). The swab was immediately streaked onto a blood-agar plate (trypticase soy agar with 5% sheep's blood, BBL Microbiology Systems, Cockeysville, Md). A bacitracin disk (Taxo A Disc, BBL Microbiology Systems) was placed on the primary inoculum and the agar was stabbed in several areas. After overnight aerobic incubation at 37°C, the plate was examined for the presence of β-hemolytic streptococci. β-Hemolytic streptococci that were sensitive to bacitracin were presumptively identified as belonging to group A. If the sensitivity to bacitracin could not be determined after overnight incubation, either because of the number or location of the β-hemolytic colonies, representative colonies were subcultured and the sensitivity to bacitracin was determined on a secondary plate. Grouping was later confirmed by the Streptex test (Wellcome Reagents, Dartford, England).

At the initial visit patients were randomly assigned to receive either 250 mg of penicillin V three times daily (250 mg/5 mL suspension) or 750 mg of penicillin V once daily (250 mg/5 mL suspension). All patients were asked to return in 18 to 24 hours for a follow-up visit, at which time they were reevaluated by the same physician who had performed the initial assessment and who was unaware of which treatment regimen had been instituted. The results of the throat culture were then determined. In patients with a negative throat culture, administration of the antibiotic was discontinued and the patients were not evaluated further. In patients with a throat culture positive for GABHS, repeated throat cultures were performed and serum specimens were obtained. These patients were instructed to continue the assigned antibiotic regimen for a full ten days. Patients returned for additional follow-up visits four to six and 14 to 21 days after completing

Accepted for publication Nov 4, 1988.

From the Departments of Pediatrics (Drs Gerber, Randolph, and Feder and Ms DeMeo) and Family Medicine (Dr Feder), University of Connecticut School of Medicine, Farmington; and the Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis (Dr Kaplan).

Reprint requests to Department of Pediatrics, University of Connecticut Health Center, Farmington, CT 06032 (Dr Gerber).

antibiotic therapy, or if any signs or symptoms suggestive of GABHS pharyngitis recurred. At these visits a repeated throat culture was obtained by using a diagnostic culture kit (Detekta-Kit Inc, Rocky Hill, Conn) that has been shown to increase significantly the recovery of GABHS from throat cultures when compared with blood-agar plates.[8] Any patient who received the experimental once-daily penicillin V regimen and had a positive throat culture at the 18- to 24-hour follow-up visit was immediately given a ten-day course of penicillin V administered three times daily and was excluded from further evaluation. Patients who had completed the experimental once-daily penicillin V regimen and had a positive throat culture at the four- to six-day follow-up visit or had signs or symptoms of pharyngitis with a positive throat culture at the 14- to 21-day follow-up visit were also given a ten-day course of penicillin V administered three times daily. In addition, patients who had completed the conventional penicillin regimen and had signs or symptoms of pharyngitis with a positive throat culture at the four- to six- or 14- to 21-day follow-up visit were given a ten-day course of penicillin V administered three times daily. Any patient who received a second course of therapy was then excluded from evaluation beyond the time of the initiation of the second course.

Acute-stage and convalescent-stage (three to four weeks later) serum specimens obtained from the patients were stored at −70°C and later were analyzed simultaneously in pairs for antistreptolysin O (ASO) and antideoxyribonuclease B (ADB) titers according to established methods.[9,10] All GABHS isolates were stored in Todd-Hewitt broth at −70°C. In patients with positive follow-up throat cultures, pretreatment and posttreatment GABHS isolates were characterized by M typing and T agglutination patterns and by serum opacity reactions according to established methods.[11,12] Bacteriologic treatment failures were defined as the presence of the same serotype of GABHS on the follow-up culture as on the initial throat culture four to six or 14 to 21 days after completing antibiotic therapy, regardless of the clinical status of the patient. Patients with a different serotype of GABHS on the follow-up than on the initial throat culture were considered to have newly acquired disease rather than a treatment failure. Compliance was determined by having a parent dip a strip of filter paper in the patient's urine on the ninth day of antibiotic therapy. This strip was allowed to air-dry and was then mailed to our laboratory and assayed for antimicrobial activity using a modification of the techniques of Markowitz and Gordis.[13]

Data were analyzed using Student's t test and χ^2 analysis.

Table 1.—Comparison of Patients in Two Treatment Groups

Characteristic	Treatment Regimen* Penicillin V 3×/d (N=76)	Penicillin V 1×/d (N=74)
Mean age, y	10.6	9.2
No. M/No. F	40/36	42/32
Duration of illness <24 h, No. (%)	52 (68)	50 (68)
Compliance, No. (%)	62 (82)	62 (84)
Antibody titer rise, No. (%)	44 (66)	35 (50)
Initial clinical findings, No. (%)		
Fever	75 (99)	72 (97)
Cervical lymphadenitis	63 (83)	66 (89)
Sore throat	74 (97)	72 (97)
Headache	60 (79)	49 (66)
Abdominal pain	20 (26)	16 (22)
Clinical improvement 24 h after initiating treatment, No. (%)	68 (89)	70 (95)

*P not significant except for age, $P=.03$.

Table 2.—Bacteriologic Response to Penicillin Therapy

Treatment Regimen	No. of Patients	No. of Positive Throat Cultures* 4-6 d After Therapy	14-21 d After Therapy	Cumulative No. (%) of Positive Follow-up Throat Cultures Treatment Failures†	Newly Acquired Diseases‡	Total
Penicillin V 3×/d	76	12	4	6 (8) [4]	10 (13)	**16 (21)**
Penicillin V 1×/d	74	13	10	16 (22) [5]	7 (9)	**23 (31)**

*Only the first positive culture is shown; repeated positive results are not included.
†Same serotype as the initial isolate. Values in brackets are the number of symptomatic patients.
‡Different serotype than the initial isolate.

RESULTS

Study patients ranged in age from 3 to 21 years (mean age, 9.8 years). Of the 225 patients from whom throat cultures were obtained, GABHS was isolated from 154 (68%), and these patients were randomly assigned to treatment groups as follows: 76 received 250 mg of penicillin V three times daily for ten days and 78 patients received 750 mg of penicillin V once daily for ten days. The patients in the two treatment groups were similar with respect to sex, duration of illness before treatment, compliance, percentage with a significant rise (≥2 dilution increment rise/≥0.2 log rise) in antistreptolysin O and/or antideoxyribonuclease B titers, clinical findings at the time of the initial visit, and clinical response to antibiotic therapy. However, patients in the three-times-daily group were significantly older ($P=.03$) than the patients in the once-daily group (Table 1). There were no major adverse reactions to either antibiotic regimen.

All 154 patients with positive throat cultures returned for the 18- to 24-hour follow-up evaluation. At this time, four (5%) of the patients in both the three-times-daily group and the once-daily group had throat cultures positive for GABHS. The four patients in the once-daily group were given a ten-day course of penicillin V three times daily and were excluded from further evaluation.

Of the remaining 150 patients with positive throat cultures, 136 (91%) returned for follow-up visits four to six days after completion of antibiotic therapy and 149 (99%) returned for follow-up visits 14 to 21 days after completion of antibiotic therapy. Overall, 39 (26%) of the 150 patients had GABHS isolated on the follow-up throat culture obtained at one of these visits (Table 2). Of the 76 patients in the three-times-daily group, 16 (21%) had GABHS isolated from one of the follow-up throat cultures: six (8%) had strains of GABHS identical to the strains isolated on their initial throat culture and were considered to have

bacteriologic treatment failures, while ten (13%) had different strains of GABHS and were considered to have newly acquired disease. Of the six patients with treatment failures, four (67%) had signs or symptoms suggestive of GABHS pharyngitis at the time of their positive follow-up throat culture. Of the 74 patients in the once-daily group, 23 (31%) had GABHS isolated on one of these follow-up throat cultures: 16 (22%) had strains of GABHS identical to the strains isolated on their initial throat cultures and were considered to have bacteriologic treatment failures, while seven (9%) had different strains of GABHS and were considered to have newly acquired disease. Of the 16 patients with treatment failures, five (31%) had signs or symptoms suggestive of GABHS pharyngitis at the time of the positive follow-up throat culture. Although the number of patients in the once-daily treatment group with positive follow-up throat cultures was greater than the number of patients in the three-times-daily treatment group (31% and 21%, respectively), this difference was not statistically significant. More importantly, the number of patients in the once-daily treatment group with bacteriologic treatment failures was significantly greater ($P = .02$) than the number of patients in the three-times-daily treatment group (22% and 8%, respectively). In addition, the number of patients in the once-daily treatment group with symptomatic treatment failures was greater than the number of patients in the three-times-daily treatment group (7% and 5%, respectively), although this difference was not statistically significant. All of the patients with treatment failures who received a subsequent ten-day course of penicillin V remained well during several months of follow-up and repeated cultures were not performed nor was treatment given again during this period.

COMMENT

In the only previously reported attempt to treat GABHS pharyngitis with a single daily dose of oral penicillin, Breese et al[5] gave 50 children a single dose of 800 000 U of buffered penicillin G potassium each day for ten days. They found that 42% of these patients had positive follow-up throat cultures during the two months after completion of penicillin therapy. In contrast, only 14% to 15% of the children with GABHS pharyngitis who had been given the same total daily dose of oral buffered penicillin G in either two or four divided doses had positive follow-up throat cultures. Although the study by Breese and colleagues[5] is weakened by the fact that serotyping of isolates was not performed and, therefore, bacteriologic treatment failures could not be distinguished from newly acquired disease, the authors concluded that a single dose of 800 000 U of buffered penicillin G given orally each day for ten days was inadequate for the treatment of GABHS pharyngitis. To our knowledge, no subsequent investigation of a once-daily oral regimen of either penicillin G or penicillin V for the treatment of GABHS pharyngitis has been performed. Evidence suggests that oral penicillin V is more active than oral penicillin G in the treatment of GABHS infections[6] and, therefore, we believed that an investigation of a regimen of once-daily penicillin V needed to be performed before the concept of once-daily penicillin therapy for GABHS pharyngitis was completely abandoned.

In the present study we have demonstrated that a 750-mg dose of penicillin V given once daily for ten days is not as effective in the treatment of GABHS pharyngitis as a 250-mg dose of penicillin V given three times daily for ten days. These two regimens were comparable in their ability to eradicate GABHS from the upper respiratory tract and in their impact on the clinical course of the disease. However, the bacteriologic treatment failure rate was significantly greater with the once-daily than with the three-times-daily regimen. Although the once-daily regimen we examined was unsuccessful despite the fact that its dosage was 50% greater than the dosage that Breese et al[5] had employed (750 mg [1.2 million U vs 800 000 U]), it is possible that an even greater once-daily dose of penicillin V would have been successful. In a preliminary investigation in which patients received 1500 mg of penicillin V once daily for ten days, we observed a 20% bacteriologic treatment failure rate, suggesting that even a doubling of the single daily dose of penicillin V would not have been effective (M.A.G., M.F.R., H.M.F., unpublished data, 1987).

That many of the positive follow-up throat cultures in both treatment groups were from newly acquired disease could be attributed to the large number of different strains of GABHS present in the community, as evidenced by the isolation of 13 different serotypes of GABHS from the study patients.

These findings support our earlier recommendation[14] as well as the current recommendation of the American Heart Association[15] that oral penicillin V be given in two or three divided doses for a full ten days for the treatment of GABHS pharyngitis.

References

1. Gerber MA, Randolph MF, Chanatry J, et al: Once daily therapy for streptococcal pharyngitis with cefadroxil. *J Pediatr* 1986;109:531-537.
2. Catanzaro FJ, Rammelkamp CH Jr, Chamovitz R: Prevention of rheumatic fever by treatment of streptococcal infections: II. Factors responsible for failures. *N Engl J Med* 1958;259:51-57.
3. Pichichero ME, Disney FA, Aronovitz GH, et al: Randomized, single-blind evaluation of cefadroxil and phenoxymethyl penicillin in the treatment of streptococcal pharyngitis. *Antimicrob Agents Chemother* 1987;31:903-906.
4. Ponte CD, Vasquez AM: Penicillin vs cefadroxil for streptococcal pharyngitis. *J Pediatr* 1987;110:663.
5. Breese BB, Disney FA, Talpey WB: Penicillin in streptococcal infections: Total dose and frequency of administration. *AJDC* 1965;110:125-130.
6. Jones WF Jr, Finland M: Blood levels from orally administered penicillin G and V: Relation to food intake. *N Engl J Med* 1955;253:754-761.
7. Randolph MF, Gerber MA, DeMeo KK, et al: Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *J Pediatr* 1985;106:870-875.
8. Randolph MF, Redys JJ, Cope JB: Evaluation of aerobic and anaerobic methods for recovery of streptococci from throat cultures. *J Pediatr* 1984;104:897-899.
9. Edwards EA: Protocol for micro antistreptolysin O determination. *J Bacteriol* 1964;87:1254-1255.
10. Nelson J, Ayoub EM, Wannamaker LW: Streptococcal antideoxyribonuclease B: Microtechnique determination. *J Lab Clin Med* 1968;71:867-873.
11. Swift HF, Wilson AT, Lancefield RC: Typing group A hemolytic streptococci by M precipitin reactions in capillary pipettes. *J Exp Med* 1943;78:127-133.
12. Williams REO: Laboratory diagnosis of streptococcal infections. *Bull WHO* 1958;19:153-176.
13. Markowitz M, Gordis L: Mail-in technique for detecting penicillin in urine: Application to the study of maintenance of prophylaxis in rheumatic fever patients. *Pediatrics* 1968;41:151-153.
14. Gerber MA, Spadaccini LJ, Wright LL, et al: Twice-daily penicillin in the treatment of streptococcal pharyngitis. *AJDC* 1985;139:1145-1148.
15. Dajani AS, Bisno AL, Chung KJ, et al: Prevention of rheumatic fever: A statement for health professionals by the Committee on Rheumatic Fever, Infective Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young. *Circulation* 1988;78:1082-1086.

Breath Hydrogen Excretion as a Screening Test for the Early Diagnosis of Necrotizing Enterocolitis

Henry W. Cheu, MD; David R. Brown, MD; Marc I. Rowe, MD

• We measured breath H_2 excretion in 122 neonates from birth to 1 month of age. The patients weighed less than 2000 g at birth and thus were at risk for developing necrotizing enterocolitis (NEC). Hydrogen excretion was normalized for the quality of the expired air by dividing by the carbon dioxide pressure of the gas sample. The mean (±SD) peak H_2/CO_2 ratio was significantly different between the seven patients who subsequently developed NEC (9.4±2.7 ppm/mm Hg) and the 115 patients who did not (5.0±3.5 ppm/mm Hg). The prevalence of NEC was 5.7% in the present study. Defining a positive test as one with a ratio value of greater than or equal to 8.0 ppm/mm Hg, the resulting screening test had a sensitivity of 86% and a specificity of 90%. The screening test yielded a 33% predictive value of a positive test and a 99% predictive value of a negative test. High H_2 excretion occurred eight to 28 hours before the earliest clinical signs of NEC. Breath H_2 excretion is a simple noninvasive test that may be useful in the management of the premature neonate at risk for the development of NEC.

(*AJDC* 1989;143:156-159)

Necrotizing enterocolitis (NEC) continues to be an important cause of morbidity and mortality among patients admitted to neonatal intensive care units (NICUs).[1] Theoretically, early diagnosis is important in caring for patients who develop NEC since it could allow earlier discontinuation of feedings and institution of antibiotic therapy, both of which may reduce the severity of disease. A specific diagnostic test would also allow the clinician to avoid withholding feedings unnecessarily from infants who do not have NEC. Currently, such a test does not exist.

Breath H_2 excretion has been used for a number of years to diagnose malabsorption and bacterial-overgrowth syndromes in adults and children[2-4] and this test has been adapted for use in neonates.[3,5] Preliminary reports have suggested that H_2 composes as much as 30% of the gas in the intestinal lumen and within the intramural blebs in patients with NEC and pneumatosis intestinalis,[6] and that increased breath H_2 excretion may occur in patients with NEC.[7-8] A recent report has demonstrated an increase in breath H_2 excretion 24 hours before the onset of clinical NEC.[9]

Herein we report the results of our experience using breath H_2 excretion as a screening test for the early diagnosis of NEC.

PATIENTS AND METHODS

All neonates admitted to the Magee-Womens Hospital (Pittsburgh) NICU during the nine months from September 1986 to May 1987 who weighed less than 2000 g at birth were eligible for the study. If parental permission was given, daily breath H_2 measurements were begun as early as the first day of life and continued for up to 1 month of age. Eighty-five percent of the eligible infants admitted to the NICU during this period were included in the study. Most were first tested before the third day of life.

A modification of the technique of Maffei et al[5] was used. Gas samples were collected from intubated infants through a modified endotracheal tube adapter that allowed one person to collect exhaled gas in a syringe while another person provided ventilatory support by hand at a rate and pressure that simulated that of the respirator. If the patient was not receiving ventilatory support from a respirator, a feeding tube (3.5- or 5-F; Sherwood Medical, St Louis) was inserted through the nose into the hypopharynx and exhaled gas was collected by coordinating withdrawal with the patient's exhalations. A 60-mL syringe (Becton-Dickinson, Rutherford, NJ) with an attached three-way stopcock (Burron Medical, Bethlehem, Pa) was used to collect and store the specimens at room temperature. All specimens were analyzed within 12 hours of collection. Previous testing using known concentrations of gas had demonstrated the stability of the storage system for as long as 72 hours. Hydrogen content in parts per million was measured on a gas chromatograph (Quintron, Milwaukee).[10] The chromatograph has a sensitivity of less than 3 ppm and an accuracy to within 3 ppm and was calibrated daily using a standard of known concentration. The carbon dioxide pressure (P_{CO_2}) was measured on a CO_2 monitor (Puritan-Bennett, Kansas City, Mo). Samples were collected daily without regard to the time of feedings since preliminary studies in which infants were tested every half hour through several feeding cycles showed no significant variation because of feeding. The type and amount of feeding, as well as antibiotic therapy, were recorded daily.

All breath H_2 values were divided by the P_{CO_2} of the sample as a means of standardizing for the quality of the expired gas.[9,11,12] The P_{CO_2} and H_2 concentrations of sequential specimens taken from the subject over a short time, by either the same or different individuals, showed coefficients of variation of 40% and 38%, respectively. The ratios of H_2/P_{CO_2} from the same data showed a coefficient of variation of only 9%. Thus, all results are presented as H_2/P_{CO_2} ratios.

We were not involved in decisions affecting the care of the infants, and no attempt was made to alter routine nutritional management. Seventy percent of the infants were fed 2.8 kJ/mL (20 kcal/oz) of formula, and the remainder were fed human milk, human milk supplemented with 2.8 kJ/mL (20 kcal/oz) of formula, or 3.4 kJ/mL (24 kcal/mL) of formula. All feedings were intermittent and were given either every two or every three hours. More than 70% of the specimens were obtained by one of us (H.W.C.). The remainder were obtained by nurses who had been trained in the technique. Specimens with a P_{CO_2} less than 10

Accepted for publication Nov 9, 1988.

From the Department of Surgery (Drs Cheu and Rowe), Children's Hospital of Pittsburgh, and the Department of Pediatrics, Magee-Womens Hospital (Dr Brown), University of Pittsburgh School of Medicine.

Reprint requests to Department of Pediatrics, Magee-Womens Hospital, Forbes Avenue and Halket Street, Pittsburgh, PA 15213 (Dr Brown).

mm Hg were considered inadequate and were repeated. If feedings were discontinued because of feeding intolerance, the time was noted. Although the diagnosis of NEC required the presence of pneumatosis intestinalis or characteristic operative findings, the time at which these patients had their feedings stopped was defined as the time of NEC diagnosis.

Data were analyzed using the t and χ^2 tests.[13]

RESULTS

A total of 2345 specimens were obtained from 122 patients. Seven of these patients had NEC diagnosed during the course of the study. The mean (±SD) birth weights and gestational ages were not statistically significantly different between the two groups. The patients with NEC weighed 1.41±0.42 kg at 31.7±2.4 weeks' gestation, while patients without NEC weighed 1.31±0.39 kg at 29.8±2 weeks' gestation.

To assess the usefulness of the breath H_2 excretion measurement as a diagnostic screening test for NEC, each patient was assigned an H_2/CO_2 ratio that corresponded to his or her highest value in the case of patients without NEC, or to the highest value obtained before the clinical suspicion of NEC in patients who were subsequently diagnosed as having NEC. The highest ratios in the infants who developed NEC occurred from eight to 28 hours (mean±SD, 16.0±6.8 hours) before the clinical suspicion of NEC, ie, eight to 28 hours before feedings were stopped. The patients with NEC were clinically well at the time highest ratios were obtained.

Of 18 patients with an H_2/PCO_2 above 8 ppm/mm Hg, six had NEC and 12 did not. Of 104 patients whose H_2/PCO_2 was less than or equal to 8.0 mm Hg, one had NEC and 103 did not. In this population, where disease prevalence was 5.7%, the sensitivity and specificity were both between 85% and 90%. The predictive values were 99% for a negative test and 33% for a positive test. Figure 1 shows each patient's highest value as well as the group means and SDs. The seven patients with NEC had a mean peak H_2/CO_2 ratio of 9.4 ppm/mm Hg. This was statistically higher than the mean peak ratio of 5.0 ppm/mm Hg for the 115 patients without NEC ($P<.005$; $t=3.29$; $df=120$). The value of 8.0 ppm/mm Hg was chosen retrospectively as the critical value because it maximized the specificity and sensitivity of this test as we developed it. We do not expect this number to stand as an unalterable value. Rather, it indicates an excessively high H_2 excretion and its absolute value may be modified as more data are collected.

Infants did not excrete H_2 until a variable number of days after their feedings were begun. Antibiotics, usually ampicillin sodium and kanamycin sulfate, were given briefly to most infants but did not appear to affect the pattern of H_2 excretion. Representative H_2 excretion patterns for two neonates with NEC and two neonates without NEC are shown in Fig 2. Feeding and antibiotic data are presented along with the simultaneously obtained H_2/CO_2 ratios. The neonates with NEC (Fig 2, left) experienced a rapid increase in their H_2/CO_2 ratios 14 and 18, hours, respectively, before feedings were discontinued. Both were either receiving antibiotics during the rise, or began taking antibiotics shortly thereafter. Typical data for neonates who did not develop NEC are illustrated in Fig 2, right. The characteristic features illustrated in Fig 2, right, are that feedings of 420 kJ/kg/d (100 kcal/kg/d) had been established for a number of days (in this case six and 14 days) before the H_2/CO_2 ratio rose, that the initial rise in the H_2/CO_2 ratio was fairly rapid, and that the increased ratio was then sustained thereafter.

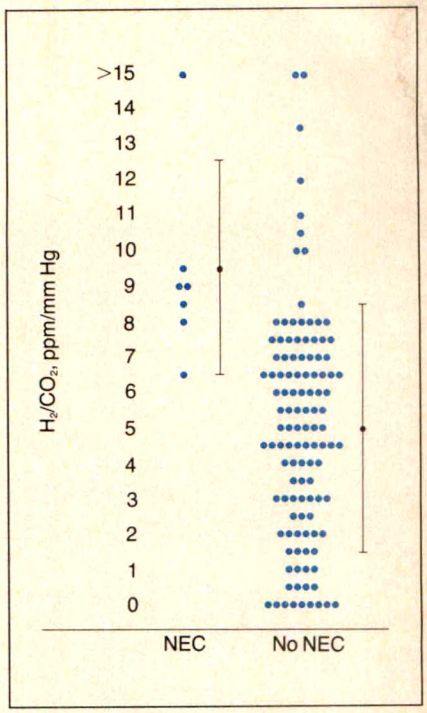


Fig 1.—Highest hydrogen/carbon dioxide ratio for patients without necrotizing enterocolitis (NEC) and highest ratio before clinical diagnosis of NEC for patients with NEC. Mean±SD for each group is plotted at right.

COMMENT

The suggestion that H_2 constitutes a large fraction of the gas seen roentgenographically and pathologically in NEC[6] has raised the possibility that H_2 excretion could be used to diagnose NEC. A recent report[9] supports this possibility based on a controlled study of eight patients with NEC and eight without NEC. The patients with NEC showed a statistically significant increase in their corrected H_2 excretion (corrected for CO_2 excretion and carbohydrate intake) during the 24 hours before the onset of NEC. Of the eight patients with NEC, only one failed to show an increase in H_2 excretion.

Our results support and extend these findings. We found a similar sensitivity with our test when we defined a pathologic increase in breath H_2 excretion as an H_2/CO_2 ratio greater than or equal to 8.0. We also obtained a sufficiently large sample to evaluate the predictive value of a test result. Although the value of a positive (high) ratio was only 33%, this result, combined with a 99% predictive value for a negative test, argues that this may be a very useful clinical diagnostic tool. Even though two patients without NEC were falsely diagnosed for every patient who was found to have the disease, a negative result furnished almost complete reassurance of the absence of NEC. Use of this test could thus prevent prolonged withholding of feedings from normal neonates who are simply experiencing transient feeding intolerance. In addition to supporting the findings of the earlier report, our testing procedure offers an added element of simplification since our data do not require correction for carbohydrate intake. In addition, this test requires approximately ten minutes for sample collection and two minutes for sample analysis, and the necessary equipment (feeding tube or endotracheal tube adapter, syringe, CO_2 analyzer, H_2 analyzer) is inexpensive to obtain and easy to use.

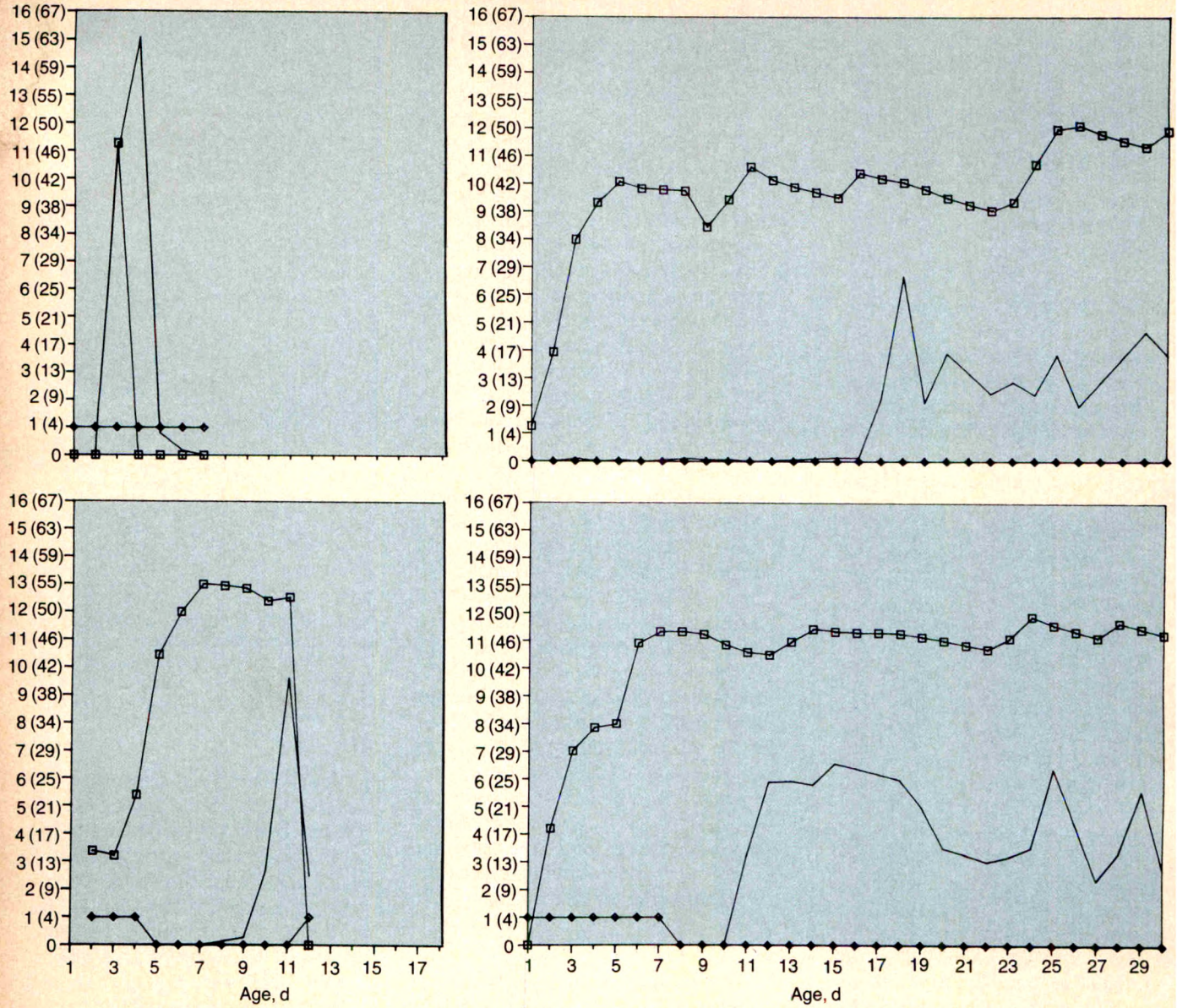


Fig 2.—Daily values for feeding (squares; parenthetical numbers indicate kilojoules/kilograms/days/10), hydrogen/carbon dioxide ratio (solid line; ppm/mm Hg), and antibiotic use (diamonds; 1 indicates yes; 0, no) in four patients. Top left, patient had necrotizing enterocolitis (NEC) diagnosed 14 hours after measurement graphed at day 3; bottom left, patient had NEC diagnosed 18 hours after measurement graphed at day 11; and top right and bottom right, data from two patients without NEC.

In addition to offering support for H_2 excretion as a diagnostic screening test, our data and the data of Garstin and Boston[9] are comparable in terms of typical H_2 excretion. Garstin and Boston[9] standardized their H_2 excretion measure to 5% CO_2 and to grams of carbohydrate intake. If our ratio of H_2/CO_2 is multiplied by 38 (millimeters of mercury/5% CO_2 at 760 mm Hg barometric pressure) and divided by the grams of carbohydrate intake, our data and theirs are comparable. An intake of 420 kJ/kg/d (100 kcal/kg/d) corresponds to approximately 11 g/kg/d of carbohydrate. Multiplying our diagnostic ratio of 8 by this fraction (38/11) gives 28 ppm as the corresponding corrected H_2 excretion, a number well within the range of the data reported by Garstin and Boston.[9] This value would increase with decreased feedings, as might be the case in a patient with impending NEC, which again is comparable with the range of 20 to 110 ppm reported by Garstin and Boston[9] in patients just before the diagnosis of NEC.

The use of CO_2 excretion to standardize H_2 excretion is logical in that it corrects for the quality of the expired gas sample, ie, it compensates for the fact that an end-tidal breath may not always be obtained. The usefulness of this procedure in yielding accurate H_2 excretion values has been tested by Perman et al,[11] who showed that as minute ventilation increased, the H_2 concentration decreased more rapidly than did the CO_2 concentration in expired gas. However,

Perman et al[11] did show that standardizing for CO_2 excretion was a valuable correction procedure at a constant minute ventilation. Although we did not measure minute ventilation in our patients, we did find the CO_2 correction was required to reduce intrapatient variability to an acceptable level.

In preliminary studies, we found that the timing of feeding did not substantially alter H_2 excretion despite the fact that data in children and adults demonstrated variation through the feeding cycle.[2,14] MacLean and Fink[15] found a great range of H_2 excretion over time and an inconsistent pattern during the feeding cycle in neonates, and Kliegman and Walsh[16] have commented that premature infants show H_2 excretion that does not vary with feedings. Our data do, however, suggest a more global relationship to feeding. As illustrated by the two normal neonates (Fig 2, right), feeding was a prerequisite for a rise in H_2 excretion, although a delay of many days occurred between the establishment of feedings and a rise in H_2 excretion. This lack of a clear relationship between H_2 excretion and the daily feeding cycle gives this screening test the advantage of being useful whenever the question of NEC arises, regardless of the time of the last feeding.

The pathogenesis of NEC, at least in part, involves gut bacterial overgrowth and/or invasion.[17-22] The premature gut malabsorbs carbohydrates,[15,23,24] thus setting the stage for possible bacterial overgrowth. It is conceivable that many premature infants undergo a period during which their gut represents an environment conducive to rapid bacterial growth. During this critical period NEC will develop if bacteria of sufficient virulence proliferate in a quantity sufficient to overcome the bowel's defenses. The degree to which the balance between bacterial growth and bacterial defenses is upset would then determine the severity of the disease, ranging from no disease or feeding intolerance to mild or fulminant NEC. This test offers the possibility of detecting bacterial overgrowth at a time before NEC is clinically apparent and thus affords the clinician the opportunity to abort disease progression in some patients.

Regardless of the specific pathogenetic interrelationships of malabsorption, gut bacterial overgrowth, and breath H_2 excretion, the H_2/CO_2 ratio, as reported herein, seems useful as a screening test for the early detection of both the presence and absence of NEC. It offers the advantage of being independent of hour-to-hour changes in feeding status and appears to be uninfluenced by the presence of antibiotics. Although the predictive value of a positive test is only 33%, this allows a sixfold to sevenfold reduction in the population at high risk for the disease (assuming a 5% prevalence and no selective diagnostic test). In addition, since the prevalence of disease in our study population (5.7%) approximately equaled the reported prevalence of NEC,[1] there should be little reduction of the predictive value of a positive test when this screening test is applied to an unselected population of premature neonates.[25] Given the apparent interrelationships of malabsorption, bacterial overgrowth, and NEC, breath H_2 excretion may also eventually yield further insight into the pathogenesis of NEC.

References

1. Holzman IR, Brown DR: Necrotizing enterocolitis: A complication of prematurity. *Semin Perinatol* 1986;10:208-216.
2. Levitt MD, Donaldson RM: Use of respiratory hydrogen (H_2) excretion to detect carbohydrate malabsorption. *J Lab Clin Med* 1970;75:937-945.
3. Douwes AC, Oosterkamp RF, Fernandes J, et al: Sugar malabsorption in healthy neonates estimated by breath hydrogen. *Arch Dis Child* 1970;55:512-515.
4. Winter HS: Breath tests as a diagnostic technique for malabsorption. *Pediatr Ann* 1987;16:259-262.
5. Maffei HVL, Metz GL, Jenkins DJA: Hydrogen breath test: Adaptation of a simple technique to infants and children. *Lancet* 1976;1:1110-1111.
6. Engel RR, Virnig NL, Hunt CE, et al: Origin of mural gas in necrotizing enterocolitis, abstracted. *Pediatr Res* 1973;7:292.
7. Kirschner BS, Lahr C, Lahr D, et al: Detection of increased breath hydrogen in infants with necrotizing enterocolitis, abstracted. *Gastroenterology* 1977;72:1080.
8. Godoy G, Truss C, Phillips J, et al: Breath hydrogen excretion in infants with necrotizing enterocolitis, abstracted. *Pediatr Res* 1986;20:348A.
9. Garstin WIH, Boston VE: Sequential assay of expired breath hydrogen as a means of predicting necrotizing enterocolitis in susceptible infants. *J Pediatr Surg* 1987;22:208-210.
10. Solomons NW, Viteri FE, Hamilton LH: Application of a simple gas chromatographic technique for measuring breath hydrogen. *J Lab Clin Med* 1977;90:856-862.
11. Perman JA, Modler S, Engel RR, et al: Effect of ventilation on breath hydrogen measurements. *J Lab Clin Med* 1985;105:436-439.
12. Niu H, Schoeller DA, Klein PD: Improved gas chromatographic quantitation of breath hydrogen by normalization to respiratory carbon dioxide. *J Lab Clin Med* 1979;94:755-763.
13. Zar JH: *Biostatistical Analysis.* Englewood Cliffs, NJ, Prentice-Hall International Inc, 1974, pp 59-65, 105-106, 151-155, 163-173.
14. Perman JA, Barr RC, Watkins JB: Sucrose malabsorption in children: Noninvasive diagnosis by interval breath hydrogen determination. *J Pediatr* 1978;93:17-22.
15. MacLean WC, Fink BB: Lactose malabsorption by premature infants: Magnitude and clinical significance. *J Pediatr* 1980;97:383-388.
16. Kliegman RM, Walsh MC: Neonatal necrotizing enterocolitis: Pathogenesis, classification, and spectrum of illness. *Curr Probl Pediatr* 1987;17:219-288.
17. Bell MJ, Feigin RD, Ternberg JL, et al: Evaluation of gastrointestinal microflora in necrotizing enterocolitis. *J Pediatr* 1978;92:589-592.
18. Popoff MR, Odette S, Ravisse P, et al: Experimental cecitis in gnotoxemic chickens monoassociated with *Clostridium butyricum* strains isolated from patients with neonatal necrotizing enterocolitis. *Infect Immunol* 1985;47:697-703.
19. Carbonaro CA, Elseciers D, Clark DA: The possible role of enterobacteria in necrotizing enterocolitis. *Pediatr Res* 1987;21:413A.
20. Musemeche CA, Kosloske AM, Bartow SA, et al: Comparative effects of ischemia, bacteria and substrate on the pathogenesis of intestinal necrosis. *J Pediatr Surg* 1986;21:536-538.
21. Kosloske AM: Pathogenesis and prevention of necrotizing enterocolitis: A hypothesis based on personal observation and a review of the literature. *Pediatrics* 1984:74:1086-1092.
22. Lawrence G, Bates J, Gaul A: Pathogenesis of neonatal necrotizing enterocolitis. *Lancet* 1982;1:137-139.
23. Weaver LT, Laker MF, Nelson R: Neonatal intestinal lactase activity. *Arch Dis Child* 1986; 61:896-899.
24. Douwes AC, Oosterkamp RF, Fernandes J, et al: Sugar malabsorption in healthy neonates estimated by breath hydrogen. *Arch Dis Child* 1980;55:512-515.
25. Vecchio TJ: Predictive value of a single diagnostic test in unselected populations. *N Engl J Med* 1966;274:1171-1173.

Quotables

Understanding: *It is not by making our brains a storehouse for cramming facts that our understanding is opened.*

M. K. GANDHI

Protein Intake and Renal Function in Children

Mitsuro Nakano, MD, PhD; Uri Alon, MD; Sandra S. Jennings, MS, RD; James C. M. Chan, MD

• To evaluate the effects of protein intake on renal tubular functions, seven metabolic studies were performed on five adolescents with mild, chronic renal insufficiency. After equilibration, patients were randomly assigned to two periods of four days each on either a high-protein diet (HPD) or a low-protein diet (LPD), with energy intakes remaining the same during both periods. High protein intake resulted in significantly higher mean (±SD) daily creatinine excretion and clearance rates. The HPD was associated with significantly increased excretion rates of potassium, phosphate, sulfate, and calcium. Net acid excretion with the HPD was nearly threefold higher than that observed with the LPD. These differences were unassociated with urinary pH, which remained similar with both diets. We conclude that different protein intakes affect urinary excretion of creatinine, potassium, phosphate, sulfate, calcium, and net acid.

(*AJDC* 1989;143:160-163)

The goals in the treatment of children with early chronic renal insufficiency are prevention of progression of renal functional deterioration and achievement of maximal growth. Because protein is an important nutrient for growth, an adequate protein intake is important in children with renal diseases. However, high protein intakes are often encountered in children with early chronic renal insufficiency,[1] which is of concern because deterioration of renal function may be related to protein-induced hyperperfusion and hyperfiltration.[2] A high-protein diet (HPD) accelerates the rate of deterioration of renal function in the diseased kidney.[2-5] On the other hand, a low-protein diet (LPD) halts or delays the progression of uremia.[6] Therefore, protein-intake restriction has been suggested as one of the potentially useful therapeutic strategies for children with early chronic renal insufficiency.[7] Dietary manipulation in these patients might have multiple effects on their metabolic status and glomerular and tubular functions. This short-term controlled crossover trial is the study of the effects of two levels of dietary protein on renal function and on acid-base, mineral, and electrolyte homeostasis in children with nonuremic chronic renal insufficiency.

Accepted for publication July 20, 1988.

From the Department of Pediatrics and Children's Medical Center (Drs Nakano and Chan), and the Clinical Research Center (Ms Jennings), Virginia Commonwealth University's Medical College of Virginia, Richmond; and the Department of Pediatrics, Children's Mercy Hospital, Kansas City, Mo (Dr Alon).

Reprint requests to Box 498, MCV Station, Richmond, VA 23298-0498 (Dr Chan).

PATIENTS AND METHODS

Seven controlled metabolic studies were performed in five adolescents with chronic renal diseases, including four female patients and one male patient, 12 to 18 years of age. Two patients were studied twice. The patients' primary renal diseases were as follows: two had chronic pyelonephritis, one had pseudohypoparathyroidism and nephrocalcinosis, one had X-linked hypophosphatemic rickets with nephrocalcinosis, and one had incompletely recovered from acute poststreptococcal glomerulonephritis suffered 18 months previously. All patients had stable kidney function during the 12 months before the studies and all were normotensive and free of urinary tract infections. The two patients with pseudohypoparathyroidism and renal hypophosphatemic rickets were treated with calcitriol (20 to 40 ng/kg/d) and also received oral supplementation (10 to 15 mg/kg/d in five divided doses) of phosphate preparation (inorganic orthophosphate). At the time of the studies these patients were normocalcemic and no modifications in drug dosage were made. The studies were conducted in the Clinical Research Center of the Medical College of Virginia, Richmond, as part of a protocol approved by the Human Research Committee. Informed consent was obtained from the parents and assent was obtained from the children.

After four days of equilibration, patients were studied for two periods of four days each; during one period an HPD was administered and during the other period an LPD was administered. The protein consisted of red meat, eggs, and dairy products, and was not a synthetic mixture. Patients were randomly assigned to begin on one or the other diet first. Two patients were studied for another eight days while on alternating diets. The LPD contained 0.5 g of protein per kilogram of body weight per day and the HPD contained 1.5 g per kilogram of body weight per day. Energy intake was adequate for growth and was kept the same for each subject while on both diets. The intake of minerals and electrolytes is shown in Table 1. In four studies the LPD was provided first and in three studies the HPD was provided first. Patients drank distilled water ad libitum. Each day at 8 AM each patient was weighed and the blood pressure was recorded.

Twenty-four hour urine specimens were collected during the last two days of each of the four-day study periods. The mean value of these two days was entered in the computation. Fasting venous blood samples were obtained at 8:10 AM on the fourth day of each period. During the urine collections, samples were kept at 4°C, mixed well, and then immediately analyzed for creatinine, sodium, potassium, chloride, calcium, phosphate, and magnesium levels; pH; net acid excretion; and titratable acid and ammonium levels. Blood was analyzed for creatinine, urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium, phosphate, total protein, and albumin levels. Analysis of urine and blood variables was done by previously described methods.[8-10]

To obtain the physiologic calcium concentration in relation to the serum protein concentration, the "corrected" serum calcium concentration was computed from the total serum protein and total serum calcium concentration, according to Parfitt's[11] formula, as follows: corrected calcium = total calcium/(0.6 + total protein/185). Fractional excretion of solutes was calculated by dividing the solute clearance by creatinine clearance. Data were analyzed for significance by Student's paired *t* test.

RESULTS

The patients tolerated the different diets well and completed all of the studies. There were no significant changes in the patients' mean body weights and blood pressures.

There were no differences in mean (±SD) serum creatinine, sodium, potassium, chloride, bicarbonate, and phosphate concentrations between the two diets. During administration of the HPD, the mean serum urea nitrogen level increased from 3.1±1.0 mmol/L to 6.3±1.6 mmol/L ($P<.01$) and the total serum calcium concentration increased from 2.35±0.11 mmol/L to 2.46±0.12 mmol/L ($P<.01$). However, as total protein and albumin concentrations also increased significantly ($P<.05$), from 62±10 g/L and 39±5 g/L to 67±8 g/L and 42±4 g/L, respectively, calculated "corrected" calcium concentrations were found to be similar with the two diets: 2.53±0.2 mmol/L with the LPD and 2.57±0.17 mmol/L with the HPD (Table 2).

High protein intake (Table 3) resulted in a significantly higher mean daily creatinine excretion rate (9.2±0.7 mmol/d/1.73 m² vs 8.1±1.1 mmol/d/1.73 m²) with the LPD ($P<.02$), and a higher mean creatinine clearance of 1.57±0.20 mL/s/1.73 m² vs 1.34±0.09 mL/s/1.73 m² ($P<.05$). These differences were independent of daily urine output, which was similar with both diets. Compared with patients on the LPD, patients on the HPD sustained significantly increased excretion rates of potassium (79.4±28.3 mmol/d/1.73 m² vs 42.7±18.4 mmol/d/1.73 m²; $P<.001$), phosphate (31.22±12.27 mmol/d/1.73 m² vs 19.76±8.49 mmol/d/1.73 m²; $P<.001$), and sulfate (16.55±3.05 mmol/d/1.73 m² vs 5.75±2.55 mmol/d/1.73 m²; $P<.001$). There were no significant differences in rates of sodium and chloride excretion nor in fractional sodium excretion. With the HPD there was a 35.4% increase in the urinary magnesium excretion rate; this difference, however, did not reach statistical significance because of large variations (Table 3).

As shown in Table 4, the mean daily urinary calcium excretion rate of 2.1±1.2 mmol/d/1.73 m² with the HPD was significantly higher than that of 1.4±0.8 mmol/d/1.73 m² with the LPD ($P<.02$). Part of the increase in urinary calcium excretion with the HPD could be attributed to the concomitant increase in the glomerular filtration rate (expressed by creatinine clearance, Table 3), but the significantly higher urinary calcium-to-creatinine ratio (0.21±0.10 vs 0.17±0.10; $P<.05$) and fractional calcium excretion (0.65%±0.23% vs 0.52%±0.24%; $P<.05$) observed during the HPD point to other factors operating along the renal tubules. In addition, the differences between the effects of the two diets on urinary calcium excretion rates were not dependent on urinary sodium excretion, as documented by the elevated urinary calcium-to-sodium ratio of 0.24±0.11 with the HPD, compared with 0.16±0.06 with the LPD ($P<0.05$), and the higher fractional calcium excretion–to–fractional sodium excretion ratio of 16.02±6.31 with the HPD, vs 9.70±4.17 with the LPD ($P<.02$).

Net acid excretion with the HPD was nearly threefold higher than that observed with the LPD (43.21±24.09 mol/d/1.73 m² vs 16.20±25.49 mol/d/1.73 m²; $P<.005$). The higher net acid excretion with the HPD was due to increased excretion of both titratable acid (12.99±12.00 mol/d/1.73 m² vs −2.09±10.59 mol/d/1.73m²; $P<.05$) and ammonium (30.45±14.48 mol/d/1.73 m² vs 18.30±15.83 mol/d/1.73m²; $P<.005$). These differences were unassociated with the urinary pH, which remained similar with both diets: 6.34±0.89 with the HPD and 6.53±0.70 with the LPD (Table 5).

Table 1.—Mean (±SD) Daily Intake of Minerals and Electrolytes in Experimental Diets

Diet	Element				
	Calcium, mmol/kg/d	Phosphorus, mmol/kg/d	Magnesium, mmol/kg/d	Sodium, mmol/kg/d	Potassium, mmol/kg/d
Low-protein	0.16±0.01	0.34±0.02	0.14±0.01	2.1±0.1	1.03±0.06
High-protein	0.41±0.03	0.79±0.04	0.21±0.01	2.2±0.1	1.76±0.05

Table 2.—Comparison of Effects of Diet on Serum Biochemical Variables*

Variable	Diet		P
	Low-Protein	High-Protein	
Creatinine, μmol/L	72±13	69±11	NS
Serum urea nitrogen, mmol/L	3.1±1.0	6.3±1.6	<.01
Sodium, mmol/L	145±4	144±5	NS
Potassium, mmol/L	4.3±0.3	4.4±0.3	NS
Chloride, mmol/L	109±3	107±3	NS
Bicarbonate, mmol/L	26.4±1.1	27.0±1.6	NS
Phosphate, mmol/L	1.41±0.34	1.45±0.32	NS
Total calcium, mmol/L	2.35±0.11	2.46±1.2	<.01
Total protein, g/L	62±10	67±8	<.05
Albumin, g/L	39±5	42±4	<.05
Corrected calcium, mmol/L†	2.53±0.20	2.57±0.17	NS

*Values are the mean±SD. NS indicates not significant.
†Calcium/(0.6+total protein/185), calculated according to Parfitt.[11]

COMMENT

A short-term crossover trial of HPDs (1.5 g per kilogram of body weight per day) and LPDs (0.5 g per kilogram of body weight per day) was conducted on five adolescents who showed mild reductions in their glomerular filtration rates. These patients showed two metabolic changes and one renal function change while on the HPD. The first included elevation of the serum urea nitrogen level and increased urinary excretion of phosphate, sulfate, and net acid. These substances are derived from amino

Table 3.—Comparison of Effects of Diet on Urinary Biochemical Variables*

Variable	Diet		P
	Low-Protein	High-Protein	
Creatinine, mmol/d/1.73 m²	8.1 ± 1.1	9.2 ± 0.7	<.02
Creatinine clearance, mL/s/1.73 m²	1.34 ± 0.09	1.6 ± 0.20	<.05
Sodium, mmol/d/1.73 m²	86 ± 29	81 ± 15	NS
Fractional sodium excretion, %	0.059 ± 0.013	0.042 ± 0.010	NS
Potassium, mmol/d/1.73 m²	42.7 ± 18.4	79.4 ± 28.3	<.001
Chloride, mmol/d/1.73 m²	76.7 ± 32.9	84.2 ± 31.3	NS
Magnesium, mmol/d/1.73 m²	24.4 ± 19.4	33.1 ± 20.9	NS
Phosphate, mmol/d/1.73 m²	19.8 ± 8.5	31.2 ± 12.3	<.001
Sulfate, mmol/d/1.73 m²	5.8 ± 2.6	16.6 ± 3.1	<.001

*Values are the mean ± SD. NS indicates not significant.

Table 4.—Comparison of Effects of Diet on Urinary Calcium Measure*

Calcium Measure	Diet		P
	Low-Protein	High-Protein	
Calcium, mmol/d/1.73 m²	1.4 ± 0.8	2.1 ± 1.2	<.02
FECa, %†	0.52 ± 0.24	0.65 ± 0.23	<.05
UCa/UCr	0.17 ± 0.10	0.21 ± 0.10	<.05
UCa/UNa	0.16 ± 0.06	0.24 ± 0.11	<.05
FECa/FENa†	9.70 ± 4.17	16.02 ± 6.31	<.02

*FE indicates fractional excretion; Ca, calcium; Cr, creatinine; and Na, sodium. Values are the mean ± SD.

†Based on corrected serum calcium concentrations: total Ca/(0.6 + total protein/185), calculated according to Parfitt.[11]

Table 5.—Comparison Between Effects of Diet on Urinary pH, Net Acid Excretion, Titratable Acid, and Ammonium*

Variable	Diet		P
	Low-Protein	High-Protein	
pH	6.53 ± 0.70	6.34 ± 0.89	NS
Net acid excretion, mmol/d/1.73 m²	16.20 ± 25.49	43.21 ± 24.09	<.005
Titratable acid, mmol/d/1.73 m²	−2.09 ± 10.59	12.99 ± 12.00	<.05
Ammonium, mmol/d/1.73 m²	18.30 ± 15.83	30.45 ± 14.48	<.005

*Values are the mean ± SD. NS indicates not significant.

acids of protein and the increases are attributed to the higher protein loading. Increased urinary calcium and magnesium excretion were also observed and these increases are related to the higher calcium and magnesium content of the HPD (Table 1), as well as to the effect of the dietary anion composition on urinary calcium excretion.[3,12,13] The second change was the increase of the serum total calcium concentration, total protein level, and albumin level. An increased serum albumin level decreases with low protein intake and presumably the serum albumin level increases with a high protein intake. The corrected calcium concentration was normal, so the increase in our patients is attributed to the associated elevation of the serum albumin level, ie, the calcium-binding protein.

The third functional change was the increase in creatinine clearance and urinary excretion of creatinine. Creatinine, a metabolite of creatine phosphate of muscle, is excreted by the kidney and its rate of production is almost constant and is not affected by protein intake. The glomerular filtration rate and renal blood flow are increased a few hours after a protein-rich meal in human adults[9] and children[3,4] and in experimental studies,[5] and/or after amino acid loading.[14-16] Although the mechanisms of the increment after protein and amino acid loading are not clear, glucagon secreted from pancreatic α-cells may act as a mediator.[17] Other mediators such as growth hormone and prostaglandin have also been suggested.[2] Finally, the increased creatinine excretion after protein intake may be due to extracellular fluid expansion from the increased sodium chloride intake associated with protein consumption.[18,19] However, the sodium intakes were the same in both groups (Table 1) and the sodium chloride excretion remained unchanged (Table 3); furthermore, the body weight and blood pressure did not change. These findings support the balanced-diet characteristic of the study.

The urinary excretion of electrolytes, calcium, phosphate, and magnesium following low and high protein intake is not unexpected in view of the dietary intake. In addition, the rise in urinary acid excretion is commensurate with the increased dietary phosphate intake. The urinary calcium data indicate that the increase is not just due to an increased filtered load of calcium but is a true reflection of different renal tubular handling of calcium because of the two diets.[12,13] The kaliuresis accompanying the high protein intake is likely a reflection of the increased sulfate excretion. As a negatively charged anion, sulfate may obligate increased renal excretion of net acid. Sodium sulfate stimulates protein secretion in the distal tubule.[3]

Our patients did not have proteinuria and their glomerular filtration rates were only mildly reduced. In the past, protein restriction was used to prevent and reverse the uremic symptoms of patients with chronic renal failure. Potassium restriction is likely one of the important management strategies for children with nonuremic chronic renal insufficiency. However, the nutritional therapy for children with chronic renal insufficiency must be studied longitudinally in children at home, where a diet acceptable to

the child and family, in terms of both the ease of preparation and palatability, would increase long-term compliance. Although the National Academy of Sciences recommends a protein intake of 0.8 g per kilogram of body weight per day for adults,[20] the average protein intake of the current American population is 1.4 g per kilogram of body weight per day,[7] close to the amount in the HPD in the present study (1.5 g per kilogram of body weight per day). We conclude that the protein intake of 1.5 g per kilogram of body weight per day, which is the average intake of American children with chronic renal insufficiency, may be excessive and may be one of the potential risk factors in acceleration of the deterioration of renal function. Furthermore, in view of the effect of protein intake on creatinine clearance and other kidney functions, interpretation of such findings needs to take into consideration the dietary background of the patient at the time of the studies.

This study was supported in part by National Institutes of Health (Bethesda, Md) grants R01 31370 and GCRC RR 00065.

We thank Virginia Murrell for secretarial assistance and Faith S. Boyle and Martha Wellons for research assistance.

References

1. Foreman J, Abitbol C, Strife F, et al: Nutritional intake in children with renal insufficiency: A report of the Growth Failure in Children With Renal Disease Study, abstracted. *Pediatr Res* 1988;23:535A.

2. Jones R, Dalton N, Turner C, et al: Oral essential aminoacid and ketoacid supplements in children with chronic renal failure. *Kidney Int* 1983;24:95-103.

3. Brouhard BH, LaGrone LF, Richards GE, et al: Somatostatin limits rise in glomerular filtration rate after a protein meal. *J Pediatr* 1987;110:729-734.

4. Brouhard BH, LaGrone LF, Richards GE, et al: Short-term protein loading in diabetes with a ten year duration of disease. *AJDC* 1986;140: 473-476.

5. Friedman AL, Pityer R: Beneficial effect of moderate protein restriction on growth, renal function and survival in young rats with chronic renal failure. *J Nutr* 1986;116:2466-2477.

6. Giordano C: Protein restriction in renal failure. *Kidney Int* 1982;22:401-408.

7. Holliday M: Nutrition therapy in renal disease. *Kidney Int* 1986;30:S3-S6.

8. Chan JCM: The rapid determination of urinary titratable acid and ammonium and evaluation of freezing as a method of preservation. *Clin Biochem* 1972;5:94-98.

9. Lin SL, Chan JCM: Urinary bicarbonate: A titrimetric method for determination. *Clin Biochem* 1973;6:207-210.

10. Chan JCM, Lovinger RD, Mamunes P: Renal hypophosphatemic rickets: Growth acceleration after long-term treatment with 1,25-dihydroxyvitamin-D_3. *Pediatrics* 1980;66:445-454.

11. Parfitt AM: Chlorothiazide-induced hypercalcemia in juvenile osteoporosis and hyperparathyroidism. *N Engl J Med* 1969;281:55-59.

12. Cole DE, Zlotkin SH: Increased sulfate as an etiological factor in hypercalciuria associated with total parenteral nutrition. *Am J Clin Nutr* 1983;37:108-113.

13. Whiting SJ, Cole DE: Effect of dietary anion composition on acid-induced hypercalciuria in the adult rat. *J Nutr* 1986;116:388-394.

14. Pitts R: The effects of infusing glycine and or varying the dietary protein intake on renal hemodynamics in the dogs. *Am J Physiol* 1944;142:355-365.

15. Tank GW, Herrin RC: Effects of protein and amino acids upon renal function in the dog. *Am J Physiol* 1954;178:165-167.

16. Lee KE, Summerill RA: Glomerular filtration rate following administration of individual amino acids in conscious dogs. *Q J Exp Physiol* 1982;67:459-465.

17. Premen AJ, Hall JE, Smith Jr MJ: Postprandial regulation of renal hemodynamics: Role of pancreatic glucagon. *Am J Physiol* 1985;248: F656-F662.

18. Bosch JP, Saccaggi A, Lauer A, et al: Renal functional reserve in humans, effects of protein intake on glomerular filtration rate. *Am J Med* 1983;75:943-950.

19. Rosman JB, Wee PMT, Meijer S, et al: Prospective randomized trial of early dietary protein restriction in chronic renal failure. *Lancet* 1984;2:1291-1296.

20. Hellerstein S, Holliday M, Grupe WE, et al: Nutritional management of children with chronic renal failure: Summary of the task force on nutritional management of children with chronic renal failure. *Pediatr Nephrol* 1987;1:195-211.

In Other AMA Journals

JAMA

The Economic Ipact of Traumatic injuries
E. J. MacKenzie; S. Shapiro; J. H. Siegel (*JAMA* 1988;260:3290)

Student Health
K. Patrick (*JAMA* 1988;260:3301)

Renal Transplantation for Children: Another View
J. B. Reinhart, J. P. Kemph (*JAMA* 1988;260:3327)

Too Many Deaths From Diarrhea
J. Snyder (*JAMA* 1988;260:3329)

Increased Nucleated Red Blood Cell Counts in Small for Gestational Age Infants With Very Low Birth Weight

Alistair G. S. Philip, MD, FRCPE, Alison M. Tito, RNC

• We evaluated the nucleated red blood cell (NRBC) counts in all infants with very low birth weight admitted to our neonatal intensive care unit from 1983 to 1986. There were 374 infants with birth weights of 500 g to 1500 g admitted in the first 24 hours after birth, but 31 died before studies were obtained. Of the remainder, 282 were appropriate for gestational age (AGA) and 61 were small for gestational age (SGA). Over 80% of both AGA and SGA infants were inborn and were evaluated within three hours of delivery. Nucleated red blood cell counts were significantly increased in SGA infants compared with AGA infants. The percents of infants with NRBC counts higher than 4.0 and 10.0×10^9/L were 48% and 26%, respectively, in SGA infants compared with 19% and 6%, respectively, in AGA infants. Similarly, the percents of SGA infants with more than 40 or 100 NRBCs per 100 white blood cells were 62% and 36%, respectively, compared with 25% and 6%, respectively, in AGA infants. Data for specific weeks of gestation are provided and the differences were present at each gestational age. Recent data in fetuses with growth retardation, when blood was obtained directly from the fetal umbilical vein, showed an association between elevated NRBC counts and chronic hypoxemia. When increased NRBC counts are seen soon after birth, the possibility of a chronic intrauterine insult should be considered.

(*AJDC* 1989;143:164-169)

It has been known for some time that a variety of conditions may produce intrauterine "hematologic stress," resulting in large numbers of circulating nucleated red blood cells (NRBCs).[1] Although hypoxia has been mentioned as an associated factor in increasing the number of NRBCs, the most recent edition of the only monograph dealing exclusively with hematologic problems in the neonate makes no mention of intrauterine growth retardation (IUGR).[2]

As a result of the use of automated counters of blood cells, more attention may have been focused on NRBCs in recent years. This is because the nuclei of NRBCs are not distinguished from the nuclei of leukocytes. Consequently, total leukocyte counts need to be corrected after reviewing a smear to determine the differential leukocyte count and number of NRBCs. In recent years, we observed some remarkable "corrections" in infants with marked IUGR and therefore reviewed our experience with all infants with very low birth weight admitted to our neonatal intensive care unit in a four-year period.

SUBJECTS AND METHODS

All infants with birth weights of 500 g to 1500 g admitted within 24 hours of birth to the Neonatal Intensive Care Unit (NICU) of the Maine Medical Center, Portland, from 1983 to 1986 were included in the study. The great majority were inborn and were evaluated within three hours of delivery. Gestational age was determined for each infant using the Ballard modification of the Dubowitz assessment.[3] Only those infants whose birth weight fell clearly below the tenth percentile for gestational age on the Colorado curves[4] were considered small for gestational age (SGA) or were considered to have IUGR. All of these SGA infants with IUGR had the possibility of chronic intrauterine infection investigated, but none had documented viral or protozoal infection. Several also had blood and cerebrospinal fluid sent for culture because of suspected sepsis. Only two infants with IUGR had documented early-onset sepsis, both in 1985.

A complete blood cell count was performed in the hospital laboratory on each infant at the time of admission to the NICU (ie, usually within three hours and, with three exceptions, always within the first 12 hours after birth). Almost all blood samples were obtained from umbilical artery catheters, but some were drawn from peripheral veins (venipuncture). The total white blood cell (WBC) count was initially determined, and and the number of NRBCs was determined by examination of the blood smear for the differential WBC count. At least 200 WBCs were counted when elevated NRBC counts were present. The WBC count was then corrected for the NRBC count. Absolute NRBC counts were derived by multiplying the corrected WBC count by the percentage of NRBCs (ie, NRBCs per 100 WBCs). In addition, the hematocrit and other red cell indexes, as well as platelet counts, were recorded. Complicating factors in the pregnancy, delivery, or neonatal course were noted for each infant. Neurodevelopmental assessment was performed at six months and 18 months at our NICU High Risk Assessment Clinic.

Statistical evaluation was performed using χ^2 analyses to compare findings in appropriate for gestational age (AGA) and SGA infants.

RESULTS

There were 282 AGA infants and 61 SGA infants evaluated. The majority of infants were inborn, but 52 AGA infants and 11 SGA infants were transferred after birth. Only three were evaluated after 12 hours of age, two of whom were SGA, with increased NRBC counts. In addition, 31 extremely premature infants died before studies could be performed. The majority (n = 22) of these deaths occurred in 1983 and 1984.

Table 1 demonstrates the marked discrepancy in the percentage of SGA infants with elevated NRBCs per 100 WBCs or absolute NRBC counts compared with AGA infants. All differences are highly statistically significant. The differences are displayed by week of gestation in Fig 1, where the discrepancy is noted at all gestational ages. Fur-

Accepted for publication July 25, 1988.

From the Division of Neonatology, Department of Pediatrics, Maine Medical Center, Portland.

Presented in part at the Annual Meeting of the European Society for Pediatric Research, Padua, Italy, September 8, 1987.

Reprint requests to Division of Neonatology, Maine Medical Center, Portland, ME 04102 (Dr Philip).

ther comparison is displayed in Figs 2 and 3, where NRBCs per 100 WBCs and absolute NRBC count are plotted against gestational age for each group, and in Figs 4 and 5, where the same indexes are plotted against birth weight.

Despite the group differences, it is clear that some AGA infants may demonstrate marked increases in NRBCs (more than 100 NRBCs per 100 WBCs). It is noteworthy that ten of the 18 AGA infants with very high NRBC counts were equal to or less than 26 weeks' gestation (four with infection) and in four of the remaining eight, infection was implicated. There were 21 SGA infants with marked increases in NRBC counts and in most cases there was evidence of a possible hypoxic/ischemic insult (eg, severe maternal toxemia, low Apgar scores, infarcted placenta). Table 2 demonstrates the mean number of NRBCs per 100 WBCs and mean absolute NRBC count by week of gestation.

It is noteworthy that some infants did not display their maximum NRBC counts until 24 to 48 hours after birth. In infants with greatly elevated NRBC counts ($>10.0 \times 10^9$/L), levels did not return to normal until after three to 12 days.

In this population, thrombocytopenia and leukopenia were not uncommon. In SGA infants, they were usually associated with increased NRBC counts (Table 3). Although there were statistically significant differences between AGA and SGA infants, only three AGA and nine SGA infants had more than 40 NRBCs per 100 WBCs and initial platelet counts less than 100×10^9/L. Contrary to expectation, SGA infants with marked increase in NRBC counts did not demonstrate high hematocrit values and there were few neurodevelopmental abnormalities in the survivors. Only five of 48 survivors demonstrated any abnormality at 18 months of age, but follow-up data were not available for ten infants. Two infants who died with a diagnosis of sudden infant death syndrome were in the group with marked increase in NRBC counts.

Table 1.—Comparison of Percentage of Increased Nucleated Red Blood Cells (NRBCs) Between Appropriate for Gestational Age (AGA) (n = 282) and Small for Gestational Age (SGA) (n = 61) Infants

	NRBCs/100 White Blood Cells, No. (%)			Absolute NRBC Count × 10^9/L, No. (%)	
Group	>40	>100	>500	>4.0	>10.0
AGA infants	70 (25)	18 (6)	2 (1)	53 (19)	16 (6)
SGA infants	38 (62)*	21 (36)*	6 (10)*	29 (48)*	16 (26)*

*All differences between AGA and SGA infants are significant at $P<.001$, using χ^2 analysis.

COMMENT

Based on past studies, it is generally held that in cord blood from term infants

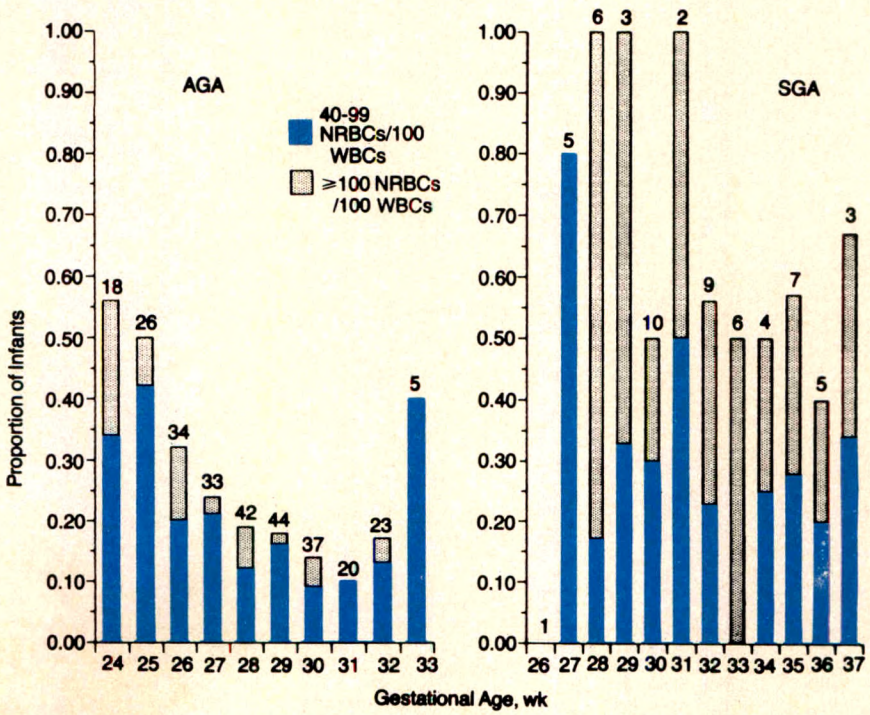


Fig 1.—Proportion of infants with increased nucleated red blood cells (NRBCs) per 100 white blood cells (WBCs) is displayed by gestational age for appropriate for gestational age (AGA) and small for gestational age (SGA) infants. Note that at all gestational ages, more SGA infants have increased NRBC counts. Numbers at top of bars indicate number of infants.

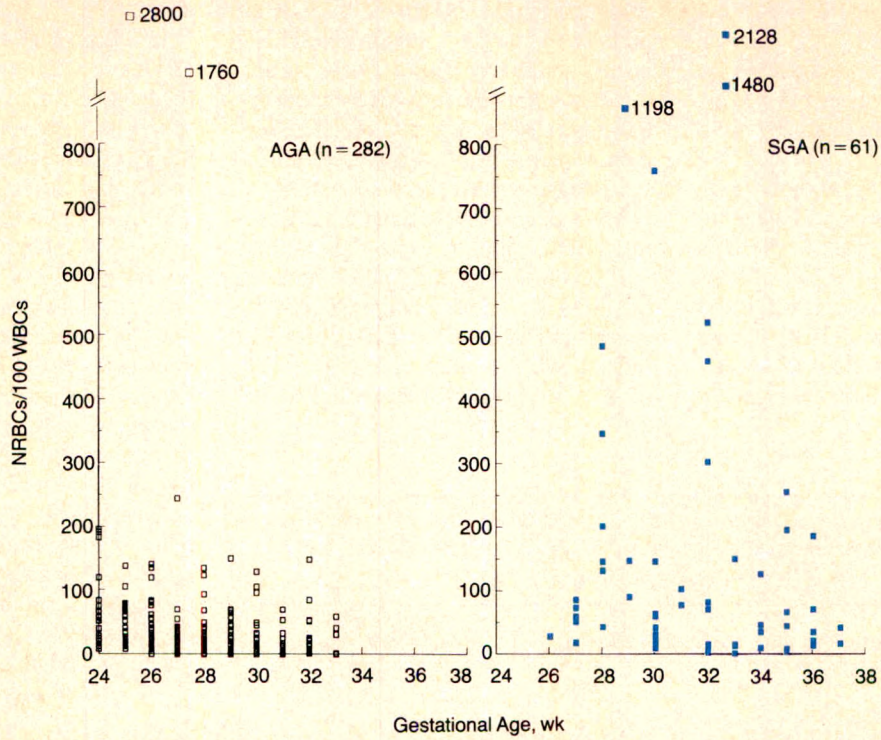


Fig 2.—Nucleated red blood cell (NRBC) counts per 100 white blood cells (WBCs) are displayed by gestational age for appropriate for gestational age (AGA) and small for gestational age (SGA) infants.

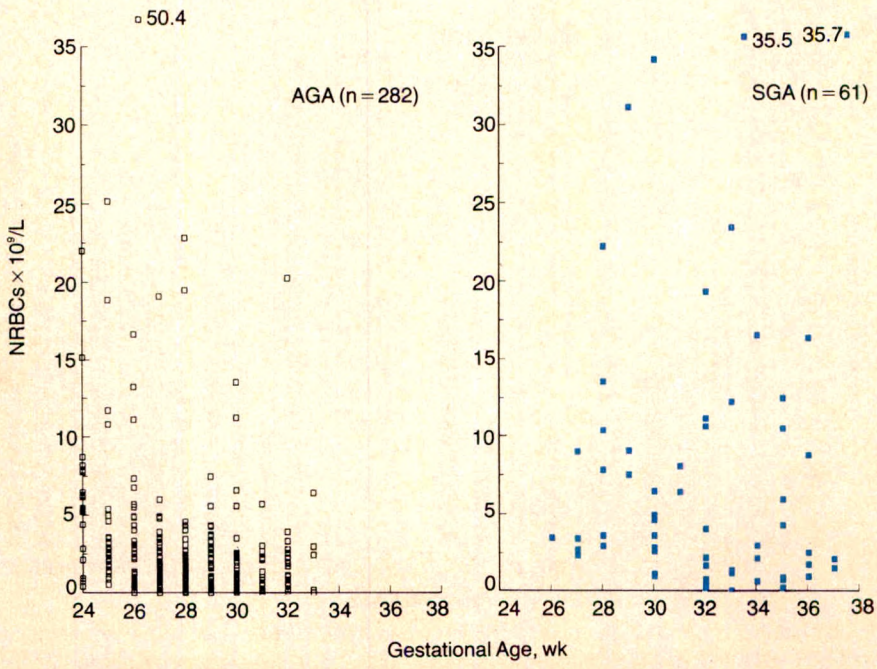


Fig 3.—Absolute nucleated red blood cell (NRBC) counts are displayed by gestational age for appropriate for gestational age (AGA) and small for gestational age (SGA) infants.

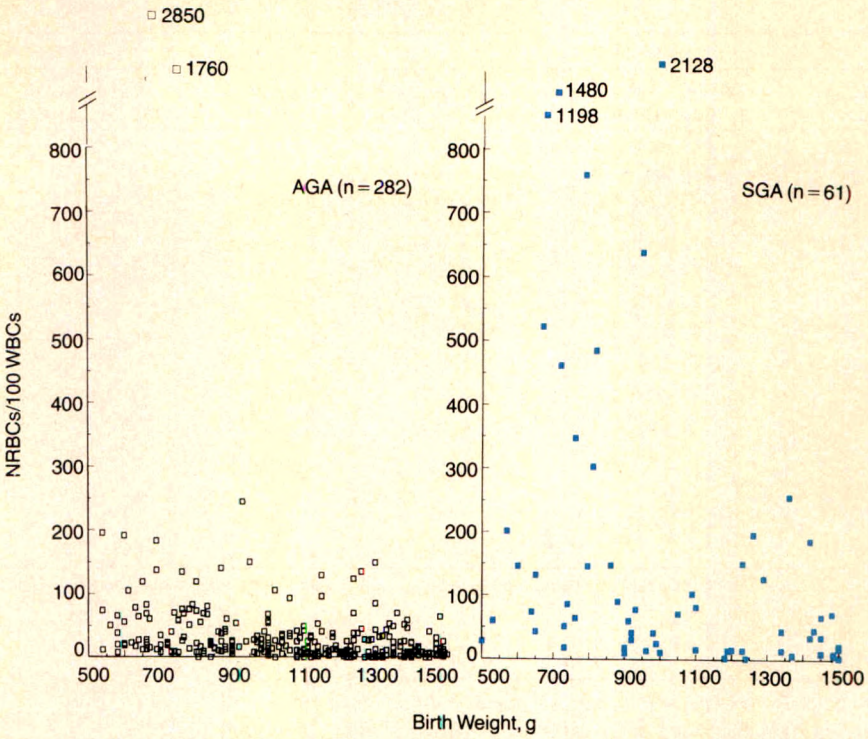


Fig 4.—Nucleated red blood cell (NRBC) counts per 100 white blood cells (WBCs) are displayed by birth weight for appropriate for gestational age (AGA) and small for gestational age (SGA) infants.

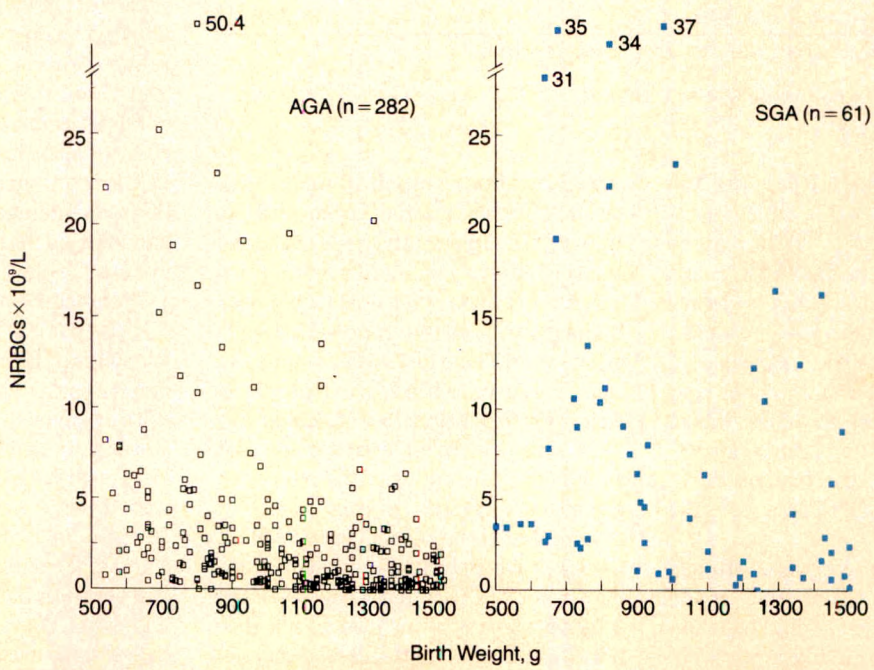


Fig 5.—Absolute nucleated red blood cell (NRBC) counts are displayed by birth weight for appropriate for gestational age (AGA) and small for gestational age (SGA) infants.

Table 2.—Mean (±SD) Nucleated Red Blood Cell (NRBC) Counts in Appropriate for Gestational Age (AGA) and Small for Gestational Age (SGA) Infants at Different Gestational Ages

Gestation, wk	AGA Infants			SGA Infants		
	No. of Infants	Mean (±SD)* of NRBCs/100 WBCs	Mean (±SD) of NRBCs × 10^9/L	No. of Infants	Mean (±SD) of NRBCs/100 WBCs	Mean (±SD) NRBCs × 10^9/L
24	18	71 (60)	6.5 (5.1)	...	...	...
25	26	46 (32)	4.7 (5.7)	...	...	...
26	34	38 (36)†	3.6 (3.8)†	1	26	3.5
27	33	32 (41)	2.8 (3.3)	5	56 (23)	4.0 (2.5)
28	42	24 (30)†	1.8 (3.1)†	6	224 (148)	10.1 (6.5)
29	44	23 (27)	1.6 (1.6)	3	478 (510)	15.9 (10.8)
30	37	21 (30)	1.8 (2.9)	10	115 (218)	6.2 (9.5)
31	20	15 (18)	1.1 (1.4)	2	89 (12)	7.2 (0.8)
32	23	23 (33)	2.2 (4.0)	9	163 (196)	5.6 (6.2)
33	5	26 (23)	2.4 (2.3)	6	631 (852)	12.3 (13.3)
34	...	...	...	4	53 (44)	5.5 (6.3)
35	...	...	...	7	81 (94)	5.0 (4.6)
36	...	...	...	5	64 (64)	6.0 (5.8)
37	...	...	...	3	231 (288)	13.1 (16.0)

*An approximation of the 95% upper confidence limit can be derived by adding 2 SDs to the mean. WBCs indicates white blood cells.
†This value is less one very high value.

Table 3.—Incidence of Thrombocytopenia and Leukopenia in Appropriate for Gestational Age (AGA) and Small for Gestational Age (SGA) Infants*

Variable	No. (%) of Infants	
	AGA (n=282)	SGA (n=61)
Initial platelet count <150 × 10^9/L	21 (7)	20 (33)†
Initial WBC count <5.0 × 10^9/L	44 (16)	16 (26)‡
Low platelet count with >40 NRBCs/100 WBCs	10 (3.5)	16 (26)†
Low WBC count with >40 NRBCs/100 WBCs	24 (8.5)	15 (25)†

*WBCs indicates white blood cells; NRBCs, nucleated red blood cells.
†$P<.001$.
‡$P<.05$ between AGA and SGA infants, using χ^2 analysis.

there are about seven NRBCs per 100 WBCs (range, zero to 25), which is approximately 0.6 × 10^9/L.[1,2] In premature infants, the mean value for NRBC count is 21 per 100 WBCs[1,2] and absolute values for NRBC counts are considered to be 1.0 to 1.5 × 10^9/L.[2] Because of variability in WBC counts, Oski and Naiman[2] believe that absolute values are more accurate. Practically speaking, however, it is more common to report the number of NRBCs per 100 WBCs.

One of the most widely quoted studies is that of Anderson[5] from 1941, which includes few infants weighing less than 2500 g and only two living infants between 1000 g and 1500 g. In the article by Playfair et al,[6] published in 1963, there were only seven values for NRBC counts in infants beyond 26 weeks' gestation. These ranged from 1.0 to 10.0 × 10^9/L. In our study, we evaluated a large number of infants with birth weights between 500 g and 1500 g. Our findings are probably representative of other populations of VLBW infants because we serve as the only tertiary level center for the entire state of Maine.

Playfair et al[6] considered it likely that a high NRBC count was "the result of a period of anoxia during delivery, though there is no definite proof of this." Others have noted that fetal hypoxia may stimulate fetal erythropoiesis and increase hemoglobin levels and red blood cell counts and decrease platelet counts, particularly in SGA infants.[7,8] These latter reports do not comment on NRBC counts, but it has been postulated that fetal hypoxemia might be responsible for the higher NRBC counts (13 ± 22 per 100 WBCs) in infants of diabetic mothers.[9] One other recent report of infants with extremely low birth weights alludes to increased NRBC counts in SGA infants in association with decreased neutrophils and platelets.[10]

Recent evidence from direct sampling of blood from the fetal umbilical vein ("cordocentesis") indicates that in growth-retarded fetuses, the increase in NRBC count is related to the severity of the hypoxic insult.[11] In 42 fetuses with IUGR between 20 and 36 weeks' gestation, the findings were remarkably similar to those noted in this study in SGA infants (Table 1), with 62%, 45%, and 14% having more than 40, 100, and 500 NRBCs per 100 WBCs, respectively (P. W. Soothill, BSc, MB,BS, written communication, January 1987).

The standard used to determine SGA status may be overstrict, so that other infants with IUGR might have been included using a different set of curves. For example, a male infant weighing 855 g at 28 weeks' gestation was classified as AGA, but was obviously borderline SGA. This infant required delivery by cesarean section for fetal distress and had 1760 NRBCs per 100 WBCs. Nevertheless, the data in AGA infants (Table 2) may provide useful starting

norms, although "true" norms may require evaluation only of infants without problems.

IMPLICATIONS

The evidence from cordocentesis in fetuses with IUGR indicates that elevated NRBC counts may reflect chronic intrauterine hypoxemia,[11] although it is not clear what duration of hypoxemia is required to produce an elevated NRBC count. It is possible that NRBC counts at birth in IUGR infants may suggest chronic hypoxemia, but the lack of a marked increase in hematocrit value may indicate a subacute insult. In AGA infants, increased NRBC count may indicate other hematologic "stress," such as infection or anemia. Although the short-term outcome (to 18 months) in the majority of the SGA infants was good, there is a possibility that a subsequent poor outcome could be related to a prenatal rather than a perinatal insult.[12] Documentation of prenatal insult may be reflected in increased NRBC counts and could prove useful in this context. Other measures, such as cord blood erythropoietin levels, might provide additional substantiating evidence.[8]

References

1. Smith CA, Nelson NM: *The Physiology of the Newborn Infant*, ed 4. Springfield, Ill, Charles C Thomas Publisher, 1976, p 269.
2. Oski FA, Naiman JL: *Hematologic Problems in the Newborn*, ed 3. Philadelphia, WB Saunders Co, 1982, p 14.
3. Ballard JL, Novak KK, Driver M: A simplified score for assessment of fetal maturation of newly born infants. *J Pediatr* 1979;95:769-774.
4. Lubchenco LO, Hansman C, Dressler M, et al: Intra-uterine growth as estimated from liveborn birth weight data at 24 to 42 weeks of gestation. *Pediatrics* 1963;32:793-800.
5. Anderson GW: Studies on the nucleated red cell count in the chorionic capillaries and cord blood of various ages of pregnancy. *Am J Obstet Gynecol* 1941;42:1-14.
6. Playfair JHL, Wolfendale MR, Kay HEM: The leucocytes of peripheral blood in the human feotus. *Br J Haematol* 1963;9:336-341.
7. D'Souza SW, Black P, MacFarlane T, et al: Haematological values in cord blood in relation to fetal hypoxia. *Br J Obstet Gynaecol* 1981;88:129-132.
8. Meberg A, Jakobsen E, Halvorsen KJ: Humoral regulation of erythropoiesis and thrombopoeisis in appropriate and small for gestational age infants. *Acta Paediatr Scand* 1982;71:769-773.
9. Mimouni F, Miodovnik M, Siddiqi TA, et al: Neonatal polycythemia in infants of insulin-dependent diabetic mothers. *Obstet Gynecol* 1986;68:370-372.
10. McIntosh N, Kempson C, Tyler RM: Blood counts in extremely low birthweight infants. *Arch Dis Child* 1988;63:74-76.
11. Soothill PW, Nicolaides KH, Campbell S: Prenatal asphyxia, hyperlactaemia, hypoglycaemia and erythroblastosis in growth retarded fetuses. *Br Med J* 1987;294:1051-1053.
12. Symonds EM: Antenatal, perinatal, or postnatal brain damage? *Br Med J* 1987;294:1046-1047.

Book Review

Paediatric Trauma, edited by E. K. Alpar and R. Owens, 247 pp, $79.50, Dobbs Ferry, NY, Sheridan House Inc, 1988.

The foreword to *Paediatric Trauma* begins, "All of us have at some time asked ourselves who should treat the injured child. Should it be a paediatrician, a surgeon, an accident physician, or even an 'orthopaedic traumatologist'? Nobody seems to know." However, the book continues, ". . . a team led by orthopedic surgeons can." It follows that this text is written from the perspective of pediatric orthopedists in its emphasis on the management of orthopedic, neural, and vascular trauma. Injuries of the head, abdomen, and thorax are covered in 44 pages of the 240-page text.

Several approaches depart from common practice in the United States, many appearing in the chapter entitled "Critical Care." The authors recommend that the child who requires full exposure for examination be covered with a blanket to prevent rapid heat loss (page 47). Although this is acceptable for field care, a radiant warmer is generally preferred for hospital management. The recommendation for initial fluid replacement for the hypovolemic child is 15 mL of "physiologic saline" per kilogram rather than the initial bolus of 20 mL/kg. The use of a flexible wire for assisting in vascular access and the Seldinger technique are not discussed. The use of oxygen and an oropharyngeal airway in the prehospital phase of care is mentioned without reference to indications for endotracheal intubation.

In the chapter entitled "Head Injuries," patients with depressed consciousness are transported in "the semiprone position," a posture that was "de riguer" in the early 1970s, being replaced recently by the rigid supine position with tight immobilization. Again, in a discussion of spinal injuries, "logrolling" is advocated, immobilization is not emphasized, and no mention of iatrogenic injury is made. The neurologic history is used to establish the time course of onset of paralysis; no concern is expressed for recurrence risk in those children with "transient" neurologic disabilities.

In the chapter entitled "Abdominal Injuries," nasogastric tube and urinary catheter placement are described without discussion of precautions in the event of cribriform plate fracture or urethral disruption. Retrograde urethrography is not mentioned.

Although the chapter on hand injuries is much longer than that on thoracic injuries, there are conspicuous omissions, such as failure to mention the phenomenon of the regrowth of distal fingertip amputations in children.

In the introduction the editors state: "It has not been our intention to be encyclopaedic . . . but rather to present practical guidance in the management of all aspects of childhood trauma" (page vii). This latter goal has been realized. *Paediatric Trauma* is a readable text with many illustrative diagrams and radiographs. It was compiled by clinicians (representing anesthesiology, radiology, and surgery) who employ a practical approach. However, all aspects of childhood trauma have not been addressed. The text falls short in being neither comprehensive in its coverage of recognition, stabilization, and management nor reliable as a single reference source.

MARTHA BUSHORE, MD
Pediatric Emergency/Critical Care Services
Good Samaritan Hospital
Flagler Drive at Palm Beach Lakes Boulevard
PO Box 3166
West Palm Beach, FL 33402-3166

CONTEMPO INTERFACE '89

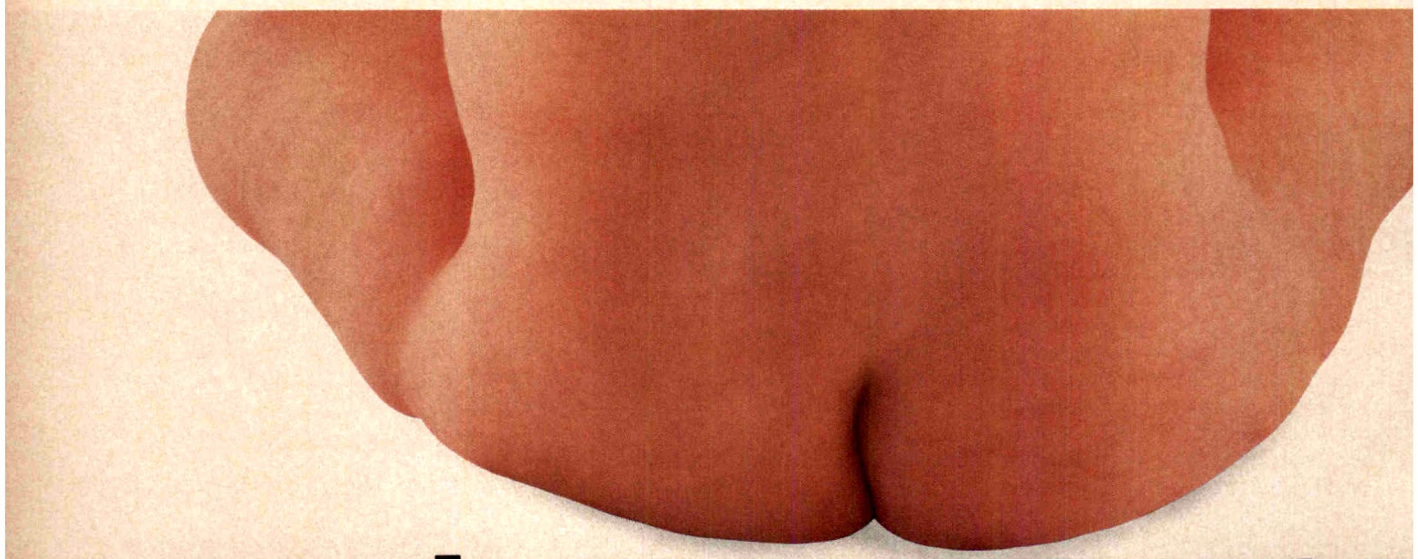
JAMA's *Contempo* issue comes life!

Survey the year's key medical advances and exchange ideas with leading physicians across the medical spectrum. There's nothing like it in continuing medical education!

CONTEMPO

interface

Call 1-800-621-8335.
(In Illinois call collect,
1-312-645-4987.)



THERE'S NO REASON TO T

ALCOHOL

Having a baby is a time to take special care of yourself. When you're pregnant, everything you eat and drink affects the child you are carrying.

Drinking beer, wine or liquor may hurt your baby. Heavy drinking can result in serious permanent mental and physical birth defects.

Alcohol is not something to be taken lightly during pregnancy. For baby's sake... and yours... the safest choice is not to drink during pregnancy.

For more information, write the National Clearinghouse for Alcohol Information, Box 2345, Rockville, MD 20852.

NIAAA NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

IS NOT FOR UNBORN BABIES

AT A CHILD LIKE AN ADULT.

Diaper rash is often treated with the same medications used to eat athlete's foot. The safety and efficacy of these more potent eroid/antifungal combinations, such as Lotrisone® (clotrimazole, SP and betamethasone dipropionate, USP),† have not been tablished in children under the age of 12.[1] Mycolog®-II, however, s been proven clinically effective even in children as young as months old.[2] Mycolog-II. It's the right way to treat a child.

ease see next page for Brief Summary of Prescribing Information.

ferences: 1. Lotrisone full Prescribing Information. 2. Mycolog-II full Prescribing Information.

spense as written.
trisone is a registered trademark of Schering Corporation, USA.

The combination steroid/antifungal specifically indicated for cutaneous candidiasis.

MYCOLOG®-II D.A.W.*

(nystatin and triamcinolone acetonide cream, USP)

SQUIBB DERM

Innovation in topical delivery

MYCOLOG®-II

Nystatin and Triamcinolone Acetonide Cream USP and Ointment

For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION: MYCOLOG-II Cream and Ointment (Nystatin and Triamcinolone Acetonide Cream USP and Ointment) for dermatologic use provide 100,000 units of the antifungal agent nystatin and 1.0 mg of the synthetic corticosteroid triamcinolone acetonide per gram.

CONTRAINDICATIONS: This preparation is contraindicated in those patients with a history of hypersensitivity to any of its components.

PRECAUTIONS: General—Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions that augment systemic absorption include application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests, and for impairment of thermal homeostasis. If HPA axis suppression or elevation of the body temperature occurs, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function and thermal homeostasis are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use).

If irritation or hypersensitivity develops with the combination nystatin and triamcinolone acetonide, treatment should be discontinued and appropriate therapy instituted.

Laboratory Tests—If there is a lack of therapeutic response, appropriate microbiological studies (e.g., KOH smears and/or cultures) should be repeated to confirm the diagnosis and rule out other pathogens, before instituting another course of therapy.

A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating hypothalamic-pituitary-adrenal (HPA) axis suppression due to corticosteroid.

Carcinogenesis, Mutagenesis, and Impairment of Fertility—Long-term animal studies have not been performed to evaluate carcinogenic or mutagenic potential, or possible impairment of fertility in males or females.

Pregnancy Category C—There are no teratogenic studies with combined nystatin and triamcinolone acetonide. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Therefore, any topical corticosteroid preparation should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Topical preparations containing corticosteroids should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers—It is not known whether any component of this preparation is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised during use of this preparation by a nursing woman.

Pediatric Use—In clinical studies of a limited number of pediatric patients ranging in age from two months through 12 years, nystatin-triamcinolone cream formulation cleared or significantly ameliorated the disease state in most patients.

Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced hypothalamic-pituitary-adrenal (HPA) axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS: A single case (approximately one percent of patients studied) of acneform eruption occurred with use of combined nystatin and triamcinolone acetonide in clinical studies.

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all age groups, even during prolonged use. Rarely, irritation may occur.

The following local adverse reactions are reported infrequently with topical corticosteroids (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermititis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

OVERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS, General); however, acute overdosage and serious adverse effects with dermatologic use are unlikely.

DOSAGE AND ADMINISTRATION: The use of these preparations should be discontinued if symptoms persist after 25 days of therapy (see PRECAUTIONS, Laboratory Tests). MYCOLOG-II Cream and Ointment should *not* be used with occlusive dressings.

HOW SUPPLIED: MYCOLOG-II Cream (Nystatin and Triamcinolone Acetonide Cream USP) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

MYCOLOG-II Ointment (Nystatin and Triamcinolone Acetonide Ointment) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

Storage—Store at room temperature; avoid freezing cream.

(J4-019A/ J4-024)

Innovation in topical delivery

SQUIBB DERM

CALIFORNIA

The Permanente Medical Group, Inc., Stockton, California, is currently recruiting for BC/BE pediatricians. There are presently seven pediatricians in the department and we are rapidly growing.

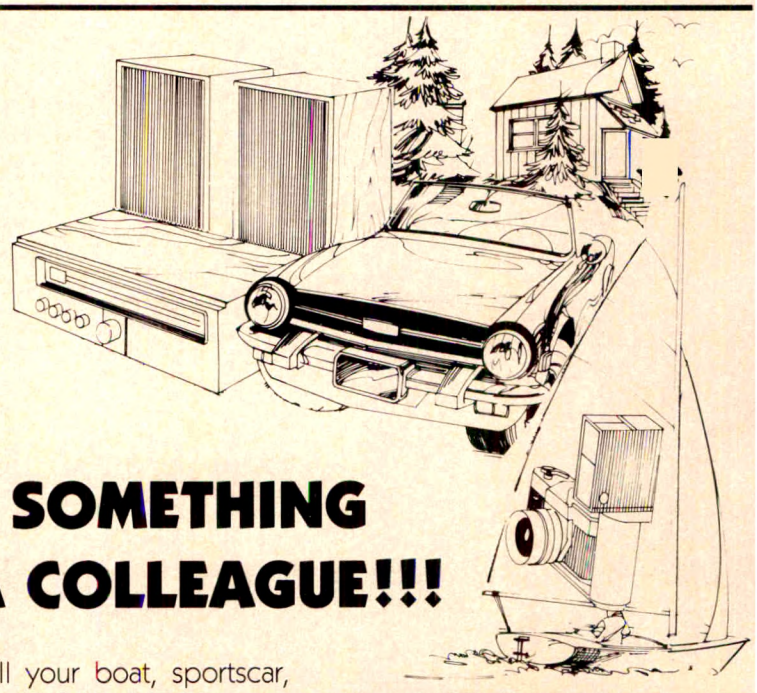
Send inquiries to:
Chief of Pediatrics
The Permanente Medical Group, Inc.
1305 Tommydon Street
Stockton, California 95210

Southeast USA
(Academic Pediatrician Wanted)

Alabama Board Certified or Board Eligible Academic Pediatrician, Assistant Professor. Teaching medical students and family practice residents, direct patient care and clinical research interests are required.

Direct inquiries with C.V. to:
David C. Hefelfinger, M.D.
Dept. of Pediatrics
700 University Blvd.
East, Tuscaloosa,
Alabama 35401
(205)348-1304

Equal Opportunity Affirmative Action Employer.



SELL SOMETHING TO A COLLEAGUE!!!

Want to sell your boat, sportscar, antiques, fine art? Want to rent your condo? Tell 300,000 colleagues about it every Friday in a CLASSIFIED AD in:

American Medical NEWS

CALL: TOLL FREE **800/237-9851** IN FLORIDA 813/443-7666

CONGENITAL ADRENAL HYPERPLASIA REFERRAL

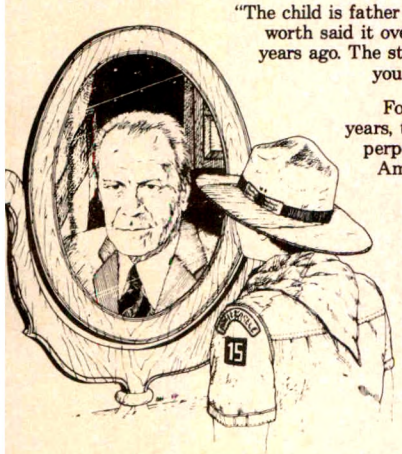
he Clinical Center requests the cooperation of hysicians in the referral of growing children ith congenital adrenal hyperplasia for a study n the relative effectiveness of once-daily ompared to twice-daily hydrocortisone dministration. The bone age must be ≤ 11 ears for boys and ≤ 9 years for girls.

atients will be followed in conjunction with heir referring physicians over the 2-year uration of the study. At the completion of the tudy patients will be returned to the care of heir referring physician. Please write or elephone:

Dr. Louisa Laue or
Dr. Gordon B. Cutler, Jr.
Building 10, Room 10N-262
National Institutes of Health
Bethesda, Maryland 20892
Tel: (301) 496-4686

REFLECTIONS OF GREATNESS

Gerald Ford, President: 1974 - 1977.
Eagle Scout, 1927.



"The child is father of the man." Wordsworth said it over one- hundred fifty years ago. The strengths ingrained in youth flourish with age.

For more than seventy years, the Boy Scouts have perpetuated the ideals of America: honor, character, loyalty; duty to God, mankind, and country.

It's not surprising some of our nation's outstanding citizens and leaders have been Boy Scouts.

BECOME A MEMBER OF THE NATIONAL BOY SCOUT ALUMNI FAMILY. — JOIN TODAY!

Your one-year, $10 membership entitles you to the Alumni Bulletin, the Annual Report, a membership card and an attractive wall certificate suitable for framing.

A three-year, $30 membership entitles you to a free Norman Rockwell print, as well as all of the benefits of a one-year membership.

Write today to:
National Boy Scout Alumni Family
1325 Walnut Hill Lane • Irving, Texas 75062 - 1296

Now, MDI therapy is available to more patients than ever before

New AeroChamber®
WITH *MASK* (aerosol holding chamber)

Permits easier metered-dose-inhaler (MDI) therapy in children and the elderly (see boxed statement below). The device consists of an aerosol holding chamber with a soft, flexible mask that covers the patient's nose and mouth. A one-way valve holds the medication until the patient inhales. Expired air is vented through exhalation ports. AeroChamber with *Mask* is economical and fits virtually any inhaler.

IMPORTANT INFORMATION
Package insert dosing instructions should be consulted for all metered dose inhalers (MDIs) when used with AeroChamber with *Mask*.
Dosage and administration recommendations vary for different MDIs, and the limitations and conditions of use for each product should be considered before utilizing this device, particularly for younger and older patients.

☐ **Yes, I am interested in the New AeroChamber® with *Mask*. Please send more information.**

AJDC 2

☐ **Enclosed is my check or money order for:**

#Units		Price		Total
_____	×	**$22.00**	=	_____

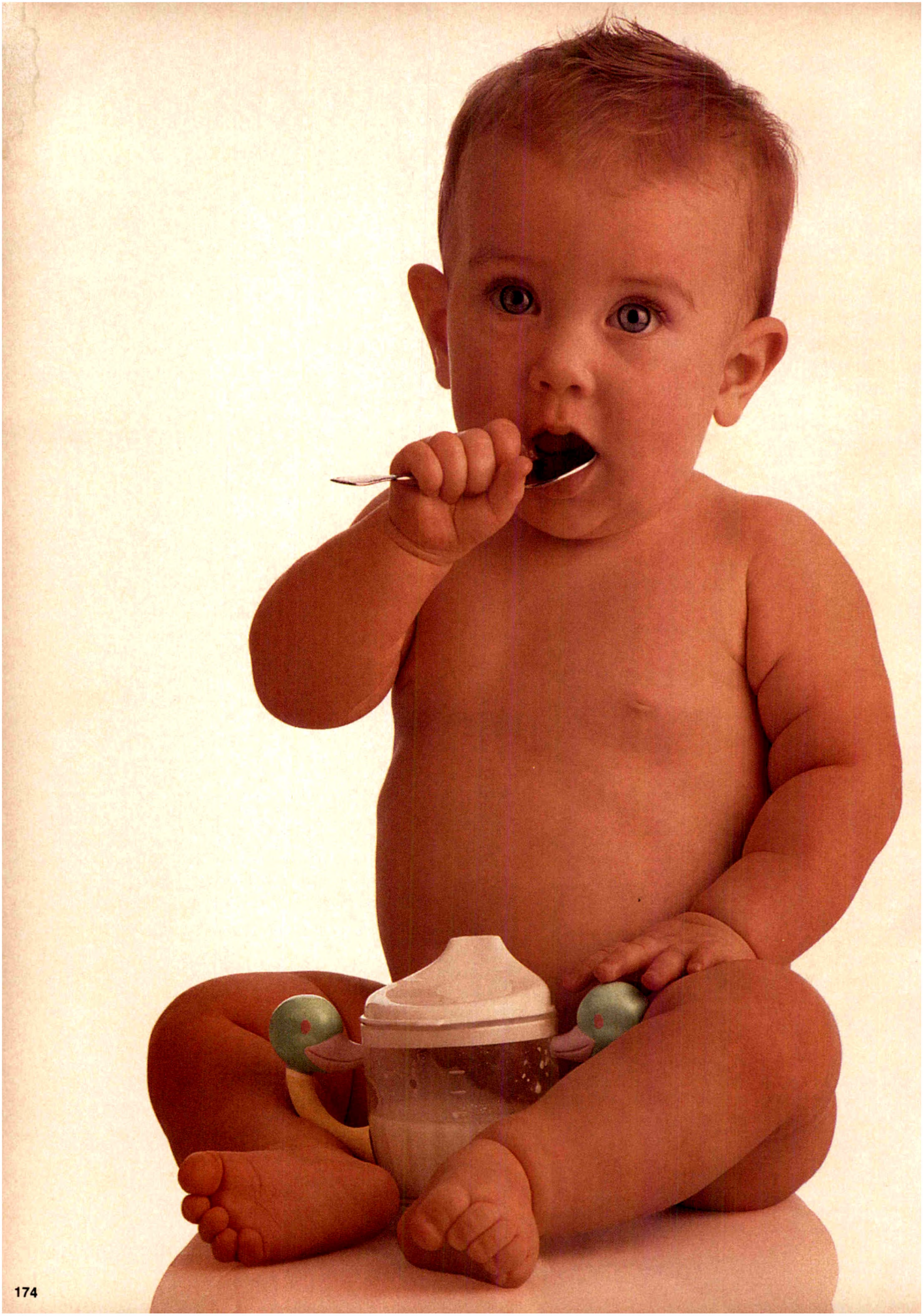
Minimum order—6 units. Price includes postage and handling.

Name _____
(please print)
Address _____
City _____
State _____ Zip _____
Phone ( ) _____

Clip and mail to: **AeroChamber® with *Mask***
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

For more information or to place an order now, call 1-800-325-1605.

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979



CARNATION® INTRODUCES

GOOD NATURE™

Iron Fortified Follow-Up Formula

For babies over six months of age
eating solid foods

Nutritionally completes baby's solid food diet. When baby reaches the solid food stage, approximately 6 months of age, formula is no longer his sole source of nutrition. Yet, the high-carbohydrate cereals, fruits, and vegetables he eats are low in certain nutrients. And, older babies require less energy from fat[1] and more from protein.[2] So, Carnation developed GOOD NATURE Follow-Up Formula, specifically designed to complement the diet of babies who are routinely eating solid food.

GOOD NATURE makes good sense. Unlike starter formula, GOOD NATURE is a follow-up formula that provides added nutrients for the older baby's optimal growth and development. GOOD NATURE contains more protein and calcium than starter formula to support the increased metabolic demands of bone mineralization and muscle mass growth.

The ratio of unsaturated to saturated fatty acids in GOOD NATURE is 2:1. GOOD NATURE is higher in monounsaturated fatty acids yet contains 28% less fat than starter formula to satisfy the changing needs of the older baby.

GOOD NATURE is good nutrition. GOOD NATURE also has a carbohydrate blend of 63% corn syrup solids and 37% lactose to help assure tolerance. It contains 12 mg iron per quart to help ensure a sufficient supply at an age when inborn stores are depleted. GOOD NATURE costs less than starter formula and also tastes, smells, and looks like the real food baby is learning to enjoy. For nutritional information, see next page.

When baby is ready for solid food, Mom may ask you about GOOD NATURE Follow-Up Formula. You can reassure her that GOOD NATURE is nutritionally sound and makes good sense for her baby.

For more information on Carnation's new GOOD NATURE Follow-Up Formula, please write to: Carnation Nutritional Products, 5045 Wilshire Blvd., Los Angeles, CA 90036.

Carnation®

GOOD NATURE Follow-Up Formula... now available to consumers in 32-fl-oz ready-to-feed fresh packs and 12-oz easy-to-mix powder canisters.

Setting the stage for better development™

GOOD NATURE™
Iron Fortified Follow-Up Formula

Stages of Baby Feeding

Birth up to 6 months

NURSING DIET
Mother's milk and/or starter formula

6 months up to 12 months

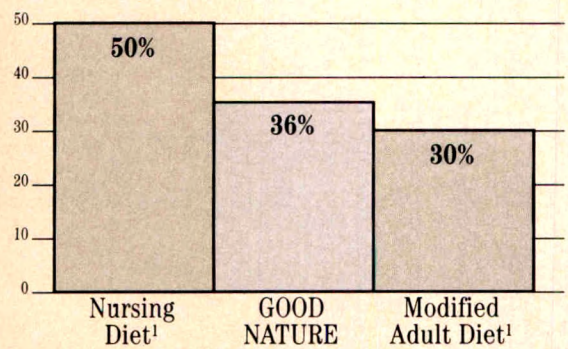
TRANSITIONAL DIET
Mother's milk and/or GOOD NATURE* with cereals, fruits, vegetables

*Not to replace breast milk. Use only when breast-feeding is not an option. Intended only for babies over 6 months of age eating solid foods.

Over 12 months

MODIFIED ADULT DIET
Cow's milk and table food

Recommended Fat Intake†



†Percentage of total caloric intake. GOOD NATURE has an optimal fat blend that is high in monounsaturated fatty acids. Unsaturated to saturated ratio is 2:1.

REFERENCES:
1. Kwiterovich PO Jr, Salz KM: Pediatric aspects of the diet-heart hypothesis, in Bond JT, Filer LJ, Leveille GA, et al (eds): *Infant and Child Feeding.* Academic Press, 1981, pp 283-315.
2. Food and Nutrition Board, NAS/MRC. *Recommended Dietary Allowances,* ed 9, 1980.

Protein Requirements During the First Year of Life[2]

Age	Average weight, kg	Protein g/kg	Requirements per day, g
0-6 months	6.0	2.2	13.2
6-12 months	9.0	2.0	18.0

Comparative Nutritional Analysis of GOOD NATURE Follow-Up Formula and Starter Formula

Nutrition information per 100 calories (5 fl oz prepared as directed)

	GOOD NATURE‡ Follow-Up Formula	Caloric Distribution (%)	Milk-Based Starter Formula§	Caloric Distribution (%)
NUTRIENTS:				
Protein	3.0 g	12.0	2.22 g	8.9
Fat	3.9 g	35.1	5.37 g	48.8
Carbohydrate	13.2 g	52.8	10.7 g	42.8
Water	134 g		133 g	
Linoleic Acid	700 mg		1,300 mg	
VITAMINS:				
Vitamin A	250 IU		300 IU	
Vitamin D	65 IU		60 IU	
Vitamin E	0.8 IU		3.0 IU	
Vitamin K	8.1 mcg		8 mcg	
Thiamine	80 mcg		100 mcg	
Riboflavin	96 mcg		150 mcg	
Vitamin B_6	66 mcg		60 mcg	
Vitamin B_{12}	0.32 mcg		0.25 mcg	
Niacin	1,280 mcg		1,050 mcg	
Folic Acid	16 mcg		15 mcg	
Pantothenic Acid	480 mcg		450 mcg	
Biotin	1.5 mcg		4.4 mcg	
Vitamin C	8 mg		9 mg	
MINERALS:				
Calcium	135 mg		75 mg	
Phosphorus	90 mg		58 mg	
Magnesium	8.4 mg		6 mg	
Iron	1.9 mg▼		1.8 mg▼	
Zinc	0.63 mg		0.75 mg	
Manganese	7 mcg		5 mcg	
Copper	76 mcg		90 mcg	
Iodine	5.7 mcg		15 mcg	
Sodium	39 mg		32 mg	
Potassium	135 mg		120 mg	
Chloride	90 mg		75 mg	

INGREDIENTS: ¶ Ⓤ NONFAT DRY MILK, CORN SYRUP SOLIDS, PALM OIL, CORN OIL, HIGH-OLEIC SAFFLOWER OIL, CALCIUM PHOSPHATE, CALCIUM CITRATE, SOY LECITHIN, POTASSIUM CITRATE, SODIUM CITRATE, SODIUM ASCORBATE, FERROUS SULFATE, MAGNESIUM CHLORIDE, ZINC SULFATE, NIACINAMIDE, ALPHA TOCOPHERYL ACETATE, CALCIUM PANTOTHENATE, COPPER SULFATE, VITAMIN A ACETATE, THIAMINE MONONITRATE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE (VITAMIN K), POTASSIUM IODIDE, VITAMIN D_3, BIOTIN, VITAMIN B_{12}.

‡All nutrients, plus the renal solute load for GOOD NATURE, are within the ranges recommended by AAP/CON for older babies.

§Based on Similac® product labeling, Ross Laboratories, 1986.

▼ The addition of iron to this formula conforms to the recommendations of AAP/CON.

¶ Easy-to-mix powder. Ready-to-feed also contains water.

Setting the stage for better development™

Carnation®

NP-022 12/88

Stress Experienced During Pediatric Residency Training

Its Causes, Consequences, Recognition, and Solutions

Robert A. Hoekelman, MD

In an EDITORIAL BOARD SPEAKS that appeared in *AJDC* last year, Ferry[1] addressed the issue of burnout experienced by pediatric residents, faculty, and practitioners. She cited the occurrence of four pediatric resident suicides in a major pediatric teaching hospital in the previous year and a 10% incidence of serious emotional difficulties among pediatric residents in four other training programs, which led those residents either to take a protracted leave of absence or to leave training altogether. These events and others led her to realize that the current structure of most pediatric residency programs can lead to an inhumane and unhealthy existence and to the potential for serious mental and physical impairment during training and later in life. She is quite correct;

See also p 181.

however, such stressful training also engenders decreased quality of medical care and of the education that residency training is supposed to provide. The subject of stress in residency training and its effects has appeared in the medical literature with increasing frequency in recent years[2-7] and has been the focus of many seminars and workshops at national medical society meetings. In addition, the American Medical Association has conducted an annual national conference on impaired health professionals since 1981; these conferences have included symposia on resident physician well-being. All state medical societies have active committees for physicians' health, and a national center and a society for professional well-being (located in Durham, NC), which deal largely with the well-being of physicians, have been operative since 1979 and 1988, respectively.

The stress residents experience during their training is not all due to the long hours they work and to the severely ill infants and children for whom they care. These are the precipitators of physical and emotional ills, but they are directed to a group of persons who are already vulnerable for the following reasons: (1) They have worked hard to gain entrance to and graduate from medical school. (Silver[8] faults medical school faculty members for their abusive treatment of medical students.) (2) They are donning the mantle of "physician" with all its real and implied responsibilities for saving lives and curing ills. (3) Most of them do so in an entirely new community filled with strangers and devoid of their personal and institutional support systems built up over the previous four or more years. (4) Many choose this time in life to marry or to have a child, which requires emotional and physical commitments to other persons—commitments that cannot be met adequately during the residency training years. (5) Most carry heavy debts and live on relatively low incomes. (6) Although they are in their middle to late 20s, they have not yet achieved independence. (7) Their parents have reached an age that makes them susceptible to serious illness, even death. (8) They are entering a highly competitive environment in which they feel compelled to perform well but do not know how they will measure up. Additionally, the three training years will be the longest of their lives in terms of total hours of being awake.

Thus, the stress to which residents are exposed is accentuated by this complex background of increased vulnerability and by the uncertainty of their futures once training is completed. The cover story of the April 25, 1988, issue of *Newsweek* (p 40) addressed the problem of stress in the workplace and rated a medical intern's job the fifth toughest, behind being an inner-city high school teacher, a police officer, a miner, and an air-traffic controller. This may be true in terms of the stress levels reached during a normal workday or work week; however, none of those other occupations require employees to work 36 or more consecutive hours or 100 to 120 hours a week, during which time high stress levels are present, at least potentially.

The life-style preparatory to and experienced during residency training is not easily changed once training is completed. More often than not, this lifestyle is carried over into clinical practice or academic medical careers. Long workdays and work weeks continue, difficulties balancing time spent in personal and family pursuits with that spent in discharging professional responsibilities persist, and the need to be the best at whatever one does remains. Chronic stress leads to the physical and emotional disturbances already noted as well as to poor marriages and high incidences of substance abuse, ill health, and suicide at rates greater than those in the general population and among members of other professions.[9]

Those of us responsible for developing

Accepted for publication Oct 31, 1988.

From the Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.

Reprint requests to Department of Pediatrics, University of Rochester, Box 777, 601 Elmwood Ave, Rochester, NY 14642 (Dr Hoekleman).

and implementing the curricula for residency training must be very sensitive to this issue to recognize the signs of stress in our residents and to use every method available to us to reduce the stress placed on them for the sake of their own well-being and for that of their patients. We have not done well in discharging this responsibility; furthermore, state medical regulatory bodies are leading the way toward reforms in residency training. Several state departments of health have implemented or will soon implement regulations that will dictate the number of consecutive hours residents may work and the cumulative number of hours they may work during specified periods of time, for example, no more than 320 hours in any four-week period (*American Medical News*, Dec 4, 1987, p 6).

The signs and symptoms of stress in residents may be subtle or overt. Ferris[10] has divided these into four categories.

1. *Physical problems* include experiencing sleep and eating disorders, demonstrating deterioration in personal hygiene and appearance, being unable to concentrate, and having multiple physical complaints and accidents, some leading to hospitalization.

2. *Family problems* include experiencing disruptive spousal relationships, including separation and divorce proceedings, impotence, and extramarital affairs; leading alternate life-styles; and withdrawing from family members.

3. *Social problems* include isolating oneself from peers, withdrawing from nonmedical activities, developing unreliable and unpredictable behavior at work and embarrassing or inappropriate behavior at parties, driving while intoxicated, and adopting excessive cause-related or religious beliefs.

4. *Work-related problems* include arriving late at work or being absent from work without explanation; losing interest in work; giving inappropriate orders and responses to telephone calls regarding patient care; spending excessive time at the hospital; and demonstrating marked behavioral changes, such as moroseness, irritability, anger, hostility, and difficulty getting along with others (patients, parents, peers, and hospital staff members).

All of these signs and symptoms are caused by working long hours and by sleep deprivation. There may also be signs of anxiety and depression that lead to a sad or flat affect, frequent crying, deterioration of performance, and substance abuse. These signs may not be initially appreciated by residents or those working with them, but over time they become obvious to their peers and to seasoned faculty members sensitive to their potential for occurrence. If they are not looked for they will be missed, and the opportunity for appropriate intervention will be lost. Stressed, anxious, and depressed residents require individual professional counseling and some alteration in their work schedule if dire consequences are to be avoided; these consequences include leaving pediatric training or medicine altogether, complete emotional breakdown, and suicide. Residency program directors must take the lead in this surveillance and ensure that all faculty members are equally alert to the problem.

When confronted by a concerned program director or other faculty member with the signs of anxiety and depression in their behavior, residents may deny that they have a problem. However, when pressed, most will admit that they are stressed, are fatigued, have feelings of self-doubt and of clinical incompetence, feel guilty when they devote time to activities not related to medicine, have come to view patients and parents as enemies who consume their time and energy and keep them from getting off work on time, and are concerned about the progression of their personal lives—achieving independence from their parents and teachers, developing significant personal relationships with others, and having children. With such admissions, these residents should be advised to obtain counseling through a prearranged program that is staffed by professionals not associated with the residency training program. If such residents refuse to seek counseling and continue to exhibit signs of anxiety and depression, they should be required to obtain counseling and should be dismissed if they do not.

Ideally, residency training should be a supportive, cooperative, joyful experience that is intellectually stimulating and paced at the learner's level. While this ideal may not always be attainable, several methods can be used to reduce the stress under which residents work and to create an environment in which residents can learn better and patients can benefit most.

These include the following:

1. Each resident should be provided with a faculty advisor who can guide during training and in career choices and can give feedback on the resident's performance gathered from written evaluations prepared by teachers and peers. Meetings to achieve these purposes should occur every two to three months throughout training. Both the department chairman and the program director should meet with all residents individually, at least annually, to review their progress and future plans, to receive their critiques of the training program, including suggested improvements, and, most important, to demonstrate a personal interest in the resident as a person and coprofessional.

2. At least four weeks of vacation should be provided during each year of training, preferably four one-week vacations spaced throughout each year. During the 1986-1987 academic year, only 32% of pediatric residency training programs in the United States did this (R.A.H., unpublished data, 1987).

3. The number of consecutive hours worked should be limited to a maximum of 29. If residents begin their work day at 7 AM and are on duty through that entire day and night, they should be allowed to go home by noon on the second day. Currently, New York state regulations prohibit residents, or any physician for that matter, from working more than 12 consecutive hours in a hospital's emergency department. It is expected that the state will at some time in the future invoke regulations that will limit to 24 the number of consecutive hours worked by residents on inpatient hospital units. It is reasonable to assume that all other states will soon follow New York's lead in restricting the number of consecutive hours residents may work in various hospital settings.

4. A system for coverage should be provided when residents need to be absent from work because of their own illness or because of an illness, death, or other crisis in the resident's family. Such sick-call resident systems are usually incorporated easily into the overall on-

call system; such a system relieves residents who are sick or have to be absent from work for other reasons from any feelings of guilt about adding to their colleagues' work load and also relieve their colleagues from the stress of assuming an increased work load.[11]

5. A reduced-schedule option should be provided for residents who wish to take prolonged periods of time off from their training so that they may engage in nonmedical activities available to them at this point in their lives and for those who want a vacation from medicine altogether. Such leaves of absence, despite prolonging the time taken to complete residency training, allow residents to gain a better perspective on medicine as a discipline and their own role within it, to focus on their career goals, to increase their self-confidence as a professional, and to gain control over their personal lives. Experience with a reduced schedule option at the University of Rochester, NY, has been very positive for both the residents and the program.[12]

6. A liberal maternity leave policy should be established that will allow residents to experience childbirth without being concerned with residency responsibilities. Paternity leave should also be provided for new fathers to enable them to support their wives and to assume the responsibility and pleasure of fatherhood.

7. The number of scheduled conferences, seminars, and didactic teaching sessions should be reduced to a minimum to allow residents to spend more time with their patients and to complete their daily medical tasks. The relative effectiveness of learning at formal presentations compared with the bedside has not been established; until it is, formal teaching sessions should be limited to presentations of essential subjects only.

8. A retreat should be conducted for all first-year residents sometime during the academic year, preferably after they have had three or four months of training. The purposes of such retreats are to provide residents with an opportunity to get to know each other better in a nonwork setting, to establish a sense of camaraderie, and to share experiences with their peers, selected faculty members, and senior residents and junior practitioners who have recently gone through the same "rites of passage." Most retreats last a full day and evening and are scheduled so that the residents are free from call both the night before and after. Some programs conduct longer retreats with more elaborate goals.[13,14]

9. Residents should be informed in no uncertain terms that moonlighting on their days and nights off is unacceptable to the training program. While it is not legally possible to prohibit moonlighting altogether, it is possible to prohibit it on any night prior to a night the resident is scheduled to be on call at the training institution. Pending state regulations limiting the number of consecutive hours and the number of cumulative hours within specified periods of time any physician may work will enable residency training program directors to prohibit moonlighting altogether.

10. Stressful rotations in intensive care units should be alternated with less-stressful rotations so that residents will not be exposed to high levels of stress over prolonged periods. It is even possible to reduce the length of assignments to these rotations from four to two weeks and schedule them more frequently throughout each training year.

11. A credentialing system should be established whereby all first-year residents must demonstrate their abilities to perform diagnostic and therapeutic procedures and to write medication orders before they are allowed to do so without supervision. Some may object to credentialing on the grounds that it deprives the resident of his or her right as a new physician to do these things independently; in fact, however, credentialing relieves the new resident of some of the stress related to being afraid of making a mistake and harming a patient in so doing. Most first-year residents can complete the full credentialing process within the first three months of training.

12. Faculty and senior residents should be urged to provide positive feedback to junior residents on their performance whenever warranted. Too often, residents receive criticism of their work for the purpose of improving it. Praise given for doing well has the same effect and does wonders in improving a resident's self-esteem.

13. A reasonable number of department-sponsored social events involving faculty and house staff should be scheduled so that a sense of belonging to the institution can be generated and so that faculty, fellows, and residents can get to know each other on a social rather than a strictly professional basis. Establishing an esprit de corps improves the functioning of the clinical service and can improve residents' self-esteem and divert them from their stressful work-related existence.

There may be other ways to reduce stress not mentioned above. For example, some programs may be able to do the following: (1) increase the number of residents in training; (2) remove some patients or patient care units from residents' care and have attending physicians provide the care with or without the assistance of nurse-practitioners or physician assistants; (3) negotiate with obstetrics/gynecology residency training program directors to have their residents fill one first-year pediatric resident position in the neonatal intensive care unit, providing their residents with valuable experience in treating high-risk newborns and reducing the number of weeks each first-year pediatric resident spends on this highly stressful unit; (4) establish a night-float system, whereby some residents work from 7 PM to 7 AM while others work only during the daytime and early evenings; (5) form resident and spousal support groups that meet regularly under the direction of a psychosocially oriented professional to discuss problems they are encountering and ways to deal with them; (6) provide financial advisers to assist residents with their fiscal problems; and (7) establish hospital-supported day-care centers for residents' children.

It may not be possible for some programs to follow all of these suggestions for reducing stress during residency training because of the small number of residents enrolled in the program and because of financial limitations; the majority of these initiatives, however, can be implemented despite these constraints.

There are those who say that reductions in the high level of intensity experienced during residency training (and the stress that accompanies it) reduce the dedication to patient care necessary

for success in medical practice and that long hours on duty provide the continuity of patient care needed to attain education and patient care of high quality.[15-17] There are no data to support this argument. Indeed, such levels of intensity and stress adversely affect learning and the care patients receive and lead to physician impairment during training and thereafter. Pediatric and other medical educators are largely responsible for these ill effects and therefore must consider how their students' lives could have been better if they had paid attention to and done something about reducing the stress placed on them during their medical training.

References

1. Ferry PC: What price glory? *AJDC* 1987;141:843.
2. McCue JD: The distress of internship: Causes and prevention. *N Engl J Med* 1985;312:449-452.
3. Hoekelman RA (ed): *Stress in Pediatric House Staff Training*. Columbus, Ohio, Ross Laboratories, 1985.
4. Smith JW, Denny WF, Witzke DB: Emotional impairment in internal medicine house staff: Results of a national survey. *JAMA* 1986;255:1155-1158.
5. McCall TB: The impact of long working hours on physicians. *N Engl J Med* 1988;318:775-778.
6. Bergman AB: Resident stress. *Pediatrics* 1988;82:260-263.
7. Resident Services Committee, Association of Program Directors in Internal Medicine: Stress and impairment during residency training: Strategies for reduction, identification, and management. *Ann Intern Med* 1988;109:154-161.
8. Silver H: Medical students and medical school. *JAMA* 1982;247:309-310.
9. McCue JD: The effects of stress on physicians and their medical practice. *N Engl J Med* 1982;306:458-463.
10. Ferris LA: Early identification and help for the impaired resident, in Robertson JJ, Vivian VL (eds): *Physician Health and Effectiveness: New Directions*. Chicago, American Medical Association, 1985, pp 116-120.
11. Parker RM, Hoekelman RA, Napodano RJ: Illnesses and other causes of unexpected absences from work during residency training. *J Med Educ* 1987;62:959-968.
12. Schaff EA, Hoekelman RA: Reduced-schedule pediatric residency training. *J Med Educ* 1984;59:817-824.
13. Bergman AB, Rothenberg MB, Telzrow RN: A 'retreat' for pediatric interns. *Pediatrics* 1979;64:528-532.
14. Doughty RA: Strategies for reducing stress: Orientation and retreats, in Hoekelman RA (ed): *Stress in Pediatric House Staff Training*. Columbus, Ohio, Ross Laboratories, 1985, pp 116-126.
15. Cousins N: Internship: Preparation or hazing? *JAMA* 1981;245:377.
16. Internship: Physicians respond to Norman Cousins. *JAMA* 1981;246:2141-2143.
17. Norman Cousins responds. *JAMA* 1981;246:2144.

A Tribute to the American Pediatric Society on its 100th Anniversary

We are gathered to celebrate for the American Pediatric Society a century.
Founded and led by Smith, Osler, Howland, Holt, and Jacobi,
The period ended by leadership of Stahlman, Barness, Katz, and Quie.

Its goals to promote children, education, and research in child health,
Fully realizing that our children are our nation's greatest wealth,
Our task to prevent disease and protect children from stealth.

We perform research on common and rare disease,
To understand even the causes of wheeze,
That children may grow, play, and enjoy life with a breeze.

Now research in nutrition lets us feed intravenous and oral;
Surgical correction of congenital defects has been successful and bold;
And many genetic diseases with our new DNA understanding unfold.

Pediatrics has led medicine in infectious disease and in prevention,
In genetic understanding, in counseling, in treatment gained attention,
And in immunology to prolong life with organ transplantation.

There is much left to research and learn to help children more.
There is still poverty, malnutrition, ignorance, infant mortality galore.
Thus we enter a new century with excitement and challenge in store.

We shall be as committed to children as the pediatricians of old,
For we are cut from the same cloth, poured into the same mold,
But we will not be here when the next century's story is told.

Billy F. Andrews, MD
May 2, 1988

Patient Care, Resident Stress, and Government Regulation

Michael I. Cohen, MD; Joseph Dancis, MD; Laurence Finberg, MD; Kurt Hirschhorn, MD; Michael Katz, MD; Edward Wasserman, MD

The Department of Health of New York State has taken the lead in addressing the problem of resident fatigue, which has been perceived as a possible cause of errors in patient care. The suggested solutions are also designed to alleviate stress among house officers due to overlong work hours with very sick patients. Different specialties have different types of problems with the proposed solution. For example, surgical residents do a certain minimum number of operations that cannot be scheduled conveniently to conform with the recommended residency schedules. In this discussion we will outline the reactions of the chairs and program directors of departments of pediatrics in the state of New York. New York may not be alone in these changes—legislation has been introduced in other states, and their health departments are considering similar recommendations. In New York the health commissioner has the mandate to regulate without additional legislation.

See also p 177.

The initial recommendation of the commission appointed by the health commissioner to look into these questions was that no resident should spend more than 16 consecutive hours on inpatient services and no more than 12 consecutive hours in the emergency department. Although the latter recommendation has already been put in place by most programs, the 16-hour inpatient limitation seemed impossible to implement because of educational activities, continuity of patient care, and insufficient staff. The staff problem is supposed to be corrected for the program scheduled to start in July 1989 by the provision of funds for hospitals to hire additional ancillary staff so that blood-sampling infusions, transportation, and the expeditious management of laboratory specimens and laboratory results will not have to be done by house officers in their reduced time. After much discussion in public and private meetings, the recommendations were changed to allow 24-hour shifts on inpatient service and to provide at least eight hours off after such a shift, at least one 24-hour day off per week, and no more than 80 hours of patient-care duties per week over any four-week period. Additional recommendations were for far greater supervision by physicians (this was begun in July 1988) and for progressive periodic approval of delineation of privileges in the various years of residency training, to be granted after demonstration of competence (this was also begun in July 1988).

We are well aware of the increased demands made on physicians as a result of modern advances in medicine. These advances have resulted in an increase in the complexity of care and, consequently, in the work load of house officers. The nights on are busier than for previous generations. In response to these changes there has been a gradual change in the schedules of work during residency training. Thus, we have seen a shift from a virtual monastic existence of continuous work with no nights off, to working every other night, to every third night, and, finally, to the current rotation of working every third or fourth night. The time freed for personal activities has permitted residents to be with their families and to read the professional literature.

In practice, these lighter work schedules have not always achieved what was intended, because a number of house officers have engaged in "moonlighting," with the consequence that they work more frequently than every fourth night; they sometimes work every other night.

There is no evidence that care has been deficient under the current system. In fact, patient care in teaching hospitals with a full complement of residents has been excellent, precisely because of the responsible participation of residents. Although we are in favor of assuring that the physicians who take care of patients are at their best, we are not convinced that arbitrary and rigid control of the number of hours of work will accomplish this goal. There are several issues that concern us.

Responsibility for care is a major consideration. Patients fare best when they have one physician directly responsible for their care. Many have no private physicians. The residents become their primary care physicians. A physician caring for a seriously ill patient cannot simply turn over this care to a colleague when the patient is still in a crisis situation; this would constitute patient abandonment. It is not proper, in our judgment, to convey the message to young physicians in training that their obligations to patients end at some stated hour regardless of the patient's condition. Worse yet, we do not think physicians should be taught that devotion to the

Accepted for publication Nov 22, 1988.

From the Departments of Pediatrics, Albert Einstein College of Medicine, Bronx, NY (Dr Cohen), New York University School of Medicine (Dr Dancis), State University of New York–Health Science Center at Brooklyn (Dr Finberg), Mount Sinai School of Medicine, New York (Dr Hirschhorn), College of Physicians and Surgeons at Columbia University, New York (Dr Katz), and New York Medical College, Valhalla (Dr Wasserman).

Reprints not available.

patient under such circumstances may actually constitute professional misconduct, as is implied in the state's recommendations.

The recommendations of the commission are directed only to physicians in the employ of hospitals. House officers, however, are preparing themselves for a career in the practice of medicine, in which the realities of life require many hours of work, often in a concentrated period. In private practice, when a patient is ill, the physician cannot simply sign over the patient to someone else. This would constitute irresponsible professional behavior.

A serious matter that has been overlooked by those who have asked for increased close supervision of residents by attending faculty is the relative knowledge and skills of the two groups of people. A resident by definition is a generalist, and, by the third and especially the fourth year of training, he or she is probably at the very peak of pediatric skills in dealing with a broad range of emergency conditions.

Practicing pediatricians, whether they are academic or in the community, begin to focus their careers either on a subspecialty or on a specific type of practice and become increasingly less familiar with most emergency situations. They do not master the new technologies for many circumstances, and their skills tend to atrophy. Among the best of us, better judgment develops from experience. For most of us, however, that experience has a much narrower focus. To imply that our senior residents are not the best physicians to deal with emergency situations in most instances is an egregious error. This in no way implies that there should be no consultation with staff who have special skills and knowledge. It is always of the utmost importance to have senior residents supervising junior ones, because at the point in a career when a physician reaches senior residency, there is probably an optimal blend of breadth and judgment, including knowing when to call for help.

If the commission's recommendations are implemented, they will have serious economic implications. Hospitals will have to either increase the number of house staff, which is contrary to the recommendations of another New York State commission, or hire other types of physicians or ancillary personnel to substitute for the residents. The types of physicians available for these jobs are not necessarily the best qualified to render care, and they are more expensive than house officers. Moreover, if the proposed plan to reduce the number of physicians becomes effective, there will not be an excess of such people. Ancillary personnel cannot provide the same level of care as residents.

In addition, certain pragmatic considerations have not been addressed. The variability of the reponsibilities of physicians among different services, different institutions, and different communities makes statewide regulations difficult to apply. How should "on-call" schedules be considered in a service in which the demands are few and sleep is possible? What would happen if a physician responsible for relieving someone whose "time is up" became ill? Who would then step in and take over? Surely, no one expects to have such physicians in reserve.

The implications of these changes would extend also to the nature of training programs. Training programs are accredited by national organizations, not governed by the regulations of particular states. Reduction in the number of hours of experience and disruption in the schedules of continuity care clinics may lead to disapproval of some training programs. These changes—or even a threat that they may take place—in turn may affect the choices of the applicants for our residency programs, who would opt for places outside of New York State.

Perhaps worst of all, a time-clock mentality pushes medicine away from being a profession toward becoming a trade, with negative implications for patients. The introduction of rigidity into the practice of medicine, which at its best is characterized by flexibility and the freedom for intelligent operation, will hamper care and will interfere with physicians' obligations to their patients. If dedication and self-sacrifice are not built into the system, we will have given up autonomy and heroism to correct for abuses by a few.

Despite the objections raised, we believe that the intent of the new regulations to provide relief from excessive fatigue and to ensure adequate supervision is laudable. It seems obvious, however, that these regulations have been hastily drawn and have overshot the mark. We intend to achieve better balance to meet all of our worthy objectives, ie, excellent patient care and excellent and efficient training programs that are both humane and *flexible*.

In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Fibrous Hamartoma of Infancy: Eight Additional Cases and A Review of the Literature

Amy S. Paller, MD; Frank Gonzalez-Grussi, MD; Joseph O. Sherman, MD (*Arch Dermatol* 1989;125:88-91)

NEW

CHILDREN'S NyQuil®

More of what puts cough and congestion to rest

For the cough and congestion that always seem to be at their worst at bedtime, now there's new CHILDREN'S NYQUIL. It's so effective at relieving symptoms that it lets children rest comfortably through the night.

CHILDREN'S NYQUIL has the maximum allowable dosage of three effective medicines: 15 mg dextromethorphan for cough control, 30 mg pseudoephedrine for decongestion, and 2 mg chlorpheniramine for rhinorrhea.

All in a great-tasting, cherry-flavored liquid that children themselves prefer 7 to 1 over the leading cough suppressant/expectorant.

For children ages 6-11, the recommended dosage is one tablespoon every 6-8 hours; ages 2-5, ½ tablespoon; under age 2, dose at your discretion.

CHILDREN'S NYQUIL.
Just what children need when they need it most.

NEW

ALCOHOL-FREE ASPIRIN-FREE

6-8 hours of symptomatic relief from each easy-to-measure dose

maximum children's dosage for restful relief

© 1988 Richardson-Vicks, Inc.
A Procter & Gamble Company

For further information about CHILDREN'S NYQUIL, call toll-free: 1-800-358-8707 (in Ohio, call 1-800-346-9101).

HE HOLDS THE TRACK RECORD AT SCHOOL.

HELP YOUR YOUNG PATIENTS BEFORE THEY START

Talk to them about illegal drug abuse.

For more information, call: (301) 468-2600
National Clearing House for Alcohol and Drug Information
Monday–Friday, 8:30 am to 4:30 pm

Partnership for a Drug-Free America

IF DIABETES IS A DISEASE YOU CAN LIVE WITH, WHY DID 150,000 DIE LAST YEAR?

Since 1 out of every 20 people has diabetes, you probably know someone who lives with it.

But what you probably don't know is what it's like to deal with diabetes: to have to stick to a diet every single day; to constantly monitor your blood sugar level; or to take insulin injections several times daily.

And you probably didn't know that diabetes can lead to other diseases, like heart disease, kidney disease and blindness.

Or, that every year 150,000 die.

Help us find a cure for diabetes. Before you know someone who dies from it.

Support the Research of the American Diabetes Association

American Diabetes Association®

Puberty in the Syndrome of Septo-optic Dysplasia

Cheryl E. Hanna, MD; Scott H. Mandel, MD; Stephen H. LaFranchi, MD

• To determine the patterns of puberty associated with the syndrome of septo-optic dysplasia, 13 older children with optic nerve hypoplasia and hypopituitarism were studied. Three patterns of puberty were observed: early, rapidly progressive puberty (group 1); appropriately timed puberty (group 2); and delayed puberty associated with gonadotropin deficiency (group 3). In the six patients in group 1, puberty began at an early bone age. Pubertal changes progressed rapidly and the bone age advanced faster than chronologic time so that, despite a normal to increased growth rate, growth potential was lost. Group 2 comprised three patients with multiple pituitary hormone deficiencies but without gonadotropin deficiency who had the timing and progression of puberty expected in hypopituitarism. The four patients in group 3, all with multiple pituitary hormone deficiencies, had gonadotropin deficiency requiring sex steroid replacement.

(*AJDC* 1989;143:186-189)

Septo-optic dysplasia is a syndrome consisting of optic nerve hypoplasia with an absence of midline brain structures, including the septum pellucidum and the corpus callosum. In 1970 the association of these abnormalities with hypopituitarism was made.[1] Since that time, septo-optic dysplasia has become a commonly recognized cause of hypopituitarism. Diagnosis and treatment of multiple pituitary hormone deficiencies in these children has allowed them to survive into the teenage and young adult years. Precocious or early puberty has been reported in two patients by Huseman et al,[2] in one patient by Margalith et al,[3] and in one of our patients.[4] Although there have been two recent descriptions of large groups of patients with this syndrome,[3,5] these groups comprise mostly preteen children. The present report describes the patterns of puberty observed in 13 older children with septo-optic dysplasia.

Accepted for publication Oct 24, 1988.

From the Department of Pediatrics, Oregon Health Sciences University, Portland.

Read before the Western Society for Pediatric Research, Carmel, Calif, Feb 18, 1988.

Reprints not available.

PATIENTS AND METHODS

The records of all children followed up in the Pediatric Endocrinology Clinic at the Oregon Health Sciences University, Portland, for growth hormone deficiency associated with optic nerve hypoplasia were reviewed. Patients were included in the study if they had spontaneous pubertal development or were receiving sex hormone replacement therapy because of gonadotropin deficiency. Patients were grouped according to the timing of their puberty. Group 1 comprised patients with clinical signs of puberty beginning earlier than anticipated (bone age <10.5 years in girls, <11.5 years in boys) and rapid progression of puberty associated with bone age advancing faster than chronologic time. Group 2 was made up of children with puberty beginning at the expected time (bone age >10.5 years in girls, >11.5 years in boys). Group 3 included children judged to be gonadotropin deficient (low serum levels of follicle-stimulating hormone and luteinizing hormone at a bone age of 12 years in girls and 13 years in boys).

Pituitary hormone deficiencies were documented using standard tests. Growth hormone deficiency was defined by a response of less than 7 μg/L to an insulin-induced hypoglycemia and arginine stimulation test or a levodopa and arginine stimulation test. Corticotropin deficiency was documented by a subnormal cortisol response during hypoglycemia that was either spontaneous or induced by insulin. Thyrotropin deficiency was demonstrated by a low total thyroxine or free thyroxine level with a normal thyrotropin level. Central diabetes insipidus was demonstrated using a standard water-deprivation test. Bone ages were determined by a single observer using the atlas of Greulich and Pyle.[6] Height predictions were made based on the method of Bayley and Pinneau.[7]

The patients were followed up for a total of 1.75 to 12 years with evaluation at four-month intervals, including assessment of puberty by Tanner stage and height measured on a wall-mounted stadiometer.

RESULTS

Six of the 13 patients with septo-optic dysplasia were included in group 1. These patients had an unusual pattern of pubertal development with clinical signs of puberty beginning at an inappropriately early bone age with rapid progression of pubertal development (Table 1). In one of these patients (patient 1), puberty was truly precocious, beginning at 5 years of age. In the other five patients, puberty began at a normal chronologic age (8 to 13 years for girls, 9 to 14 years for boys) but at an earlier bone age than expected (mean chronologic age of 11.7 years and bone age of 9.4 years for the four boys; chronologic age of 9 years for the girl, bone age delayed by two years when measured at a chronologic age of 11.4 years). Clinical signs of puberty advanced more quickly than expected, with the two girls progressing from Tanner stage II to Tanner stage III-IV in 1.3 years.[8] The two boys who reached Tanner stage III-IV did so in 2.1 years.

In all of these patients, bone age changed faster than chronologic time associated with puberty. Growth rates were normal to increased, but because the bone age advanced faster than chronologic time, these patients lost growth potential (Table 2). In the four patients who had reached Tanner stage III-IV, the predicted adult height fell from −1.9 SDs below the mean to −3.6 SDs below the mean. The two girls lost an average of 13.4 cm in predicted adult height, and the two boys lost 7.5 cm. The progressive loss of growth potential is shown in the Figure, which plots the patients' heights at their bone age. The three patients (3, 4, and 5) followed up most carefully by serial bone age determinations showed acceleration in skeletal maturation in the 1.1 to 2.3 years before clinical features of puberty became apparent (mean Δbone age/Δ

Table 1.—Timing of Pubertal Development and Description of Pituitary Hormone Deficiencies

Patient No./Age, y/Sex	Chronologic Age at Onset of Puberty, y	Bone Age at Onset of Puberty, y	Pituitary Hormone Status*				Age Growth Hormone Treatment Begun, y
			GH	TSH	Corticotropin	ADH	
Group 1							
1/7 (died)/F	5.3	7.5	–	–	–	–	Never treated
2/16.3/F	9	9.3†	–	+	+	+	12.6
3/11.5/M	11.1	10.5	–	+	+	+	6.1
4/12.0/M	11.5	10.5	–	+	+	+	11.6
5/13.1/M	10.5	10‡	–	+	+	+	2.8
6/16.5/M	13.5§	6.5	–	–	+	+	15.1
Group 2							
7/14.2/F	13.5	10.5‖	–	–	–	–	2.4
8/14.1/M	13.5	11	–	–	–	+	5.3
9/19.8/M	13.9	12	–	–	–	+	12.8
Group 3							
10/16.3/F	15.7	12	–	–	–	+	8.7
11/21.5/F	17.7	16	–	–	–	+	8.2
12/26.3/F	17.2	13	–	–	–	+	10.0
13/20.1/M	17.0	13	–	–	–	+	13.0

*GH indicates growth hormone; TSH, thyrotropin; ADH, antidiuretic hormone; plus sign, intact pituitary hormone; and minus sign, pituitary hormone deficiency.
†Bone age 9.3 years at a chronologic age of 11.4 years.
‡Bone age 10 years at a chronologic age of 9.9 years.
§When first examined at 13.5 years of age this patient had a testicular volume of 8 to 10 mL.
‖Bone age 10.5 years at a chronologic age of 12.8 years.

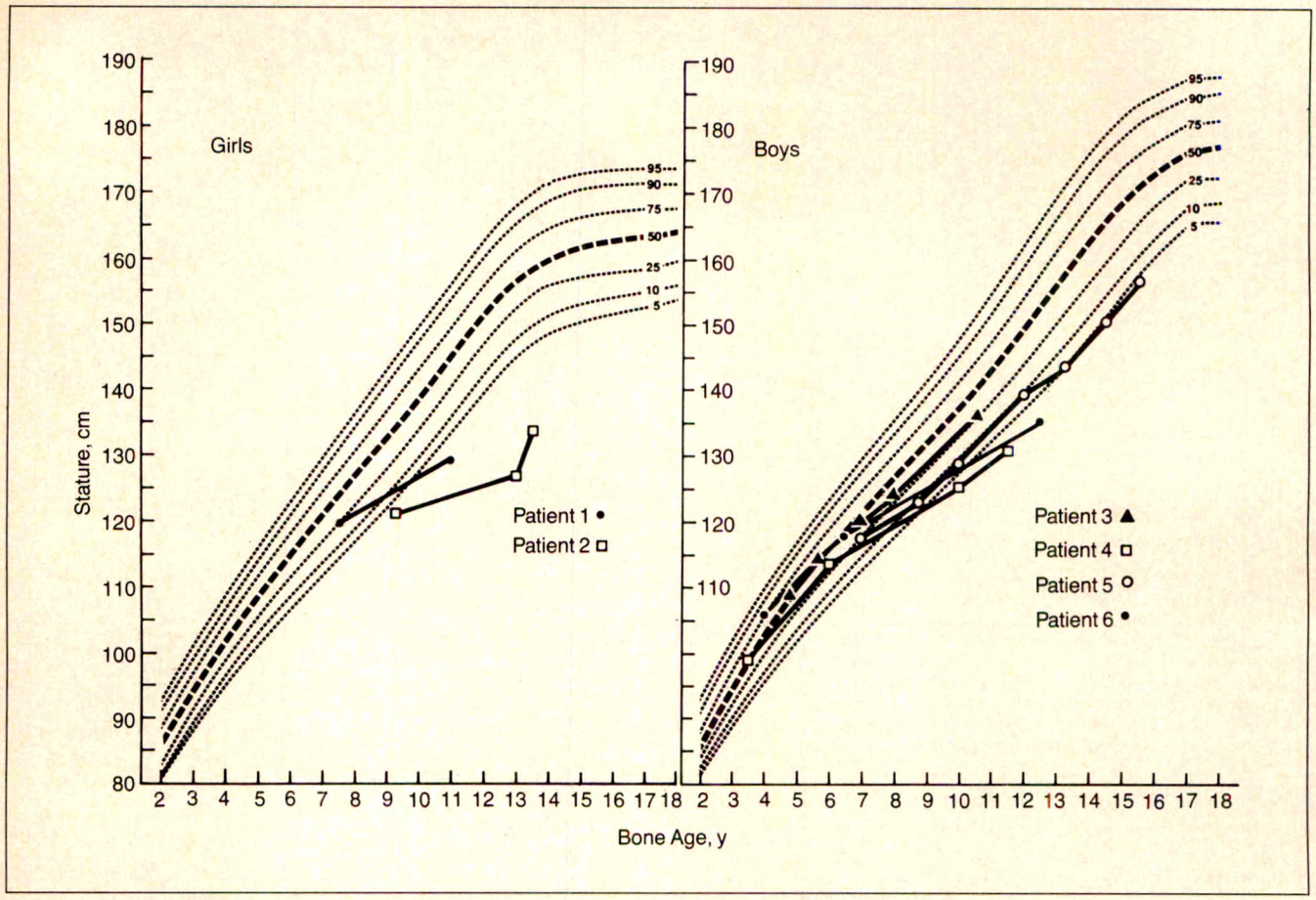
Table 2.—Growth Rates and Predicted Adult Height

Patient No.	Before Puberty		Tanner Stage II Puberty		Tanner Stage III-IV Puberty	
	Growth Rate, cm/y	Height Prediction, cm (Chronologic Age)	Growth Rate, cm/y	Height Prediction, cm	Growth Rate, cm/y	Height Prediction, cm
Group 1: early puberty						
1	. . .	. . .	5.9	149.9 (5 y 1 mo)	7.6	132.8 (6 y 11 mo)
2	. . .	. . .	4.4	142.2 (11 y 4 mo)	6.9	132.5 (12 y 7 mo)
3	5.8	167.1 (9 y 2 mo)	12.6	166.1 (11 y 1 mo)	. . .	. . .
4	5.2	166.4 (9 y 4 mo)	5.6	159.8 (11 y 7 mo)	. . .	. . .
5	5.9	169.2 (7 y 10 mo)	9.2	165.6 (11 y 1 mo)	7.3	161.5 (13 y)
6	. . .	. . .	4.7	168.1 (13 y 5 mo)	7.9	157.2 (15 y 7 mo)
Group 2: normal puberty						
7	6.1	156.3 (11 y 10 mo)	5.9	156.1 (13 y 10 mo)	. . .	. . .
8	3.7	171.5 (9 y 8 mo)	4.4	176.0 (13 y 10 mo)	. . .	. . .
9	7.5	169.7 (12 y)	5.7	173.2 (13 y 11 mo)	6.1	169.7 (17 y 3 mo)

chronologic age = 2.1). The patients who fared the worst in growth potential were those (patients 1, 2, 4, and 6) untreated with human growth hormone before puberty.

Group 2 consisted of those patients in whom the timing and progression of puberty were normal (Table 1). These patients' puberty began at a mean chronologic age of 13.75 years and a mean bone age of 11.5 years in the two boys, and a mean chronologic age of 13.8 years and and a mean bone age of 10.5 years in the girl. The progression of puberty did not appear to advance the bone age faster than chronologic time, so that predicted adult height remained constant (Table 2).

The third group consisted of four teenagers with gonadotropin deficiency (Table 1). In these patients minimal signs of puberty were present at a mean chronologic age of 16.8 years and a mean bone age of 13.7 years in the girls, and a mean chronologic age of 17 years and mean bone age 13 years in the boy. Although one of the girls (patient 11) had spontaneous breast development it did not progress beyond Tanner stage III by a bone age of 16 years. The other girls and the boy had no clinical signs of puberty. Serum gonadotropin and sex hormone values were low and replacement with sex steroids was instituted. Mean final adult height in the three female patients was 142.9 cm and in the male



Progressive loss of growth potential as demonstrated by serial height measurements plotted at bone age at time of measurement.

patient it was 157.5 cm. These short adult heights in part reflect suboptimal growth hormone treatment.

The presence of multiple pituitary hormone deficiencies, occurring in nine of 13 patients with septo-optic dysplasia, were associated with all three patterns of puberty. All four of the patients with isolated growth hormone deficiency fell into the group with early, rapidly progressive puberty. Rapid advancement of puberty was observed in both boys and girls. There was no correlation between visual handicap and pattern of puberty, with blind children being included in each group.

COMMENT

As many as two thirds of patients with multiple pituitary hormone deficiencies fail to enter puberty spontaneously because of gonadotropin deficiency.[9] Children with hypopituitarism but without gonadotropin deficiency have a delay in the timing of puberty corresponding to the delay in bone age caused by their hormone deficiencies.[10] Spontaneous puberty is not expected until the bone age advances beyond 10.5 years in girls and 11.5 years in boys.

Precocious puberty has occasionally been reported in patients with hypopituitarism from causes such as central nervous system tumors and trauma, and we have also seen it in a girl with Meckel-Gruber syndrome. Sexual precocity in girls with septo-optic dysplasia has been reported by Huseman et al[2] and LaFranchi.[4] Huseman et al[2] described two girls with early puberty and septo-optic dysplasia. One girl had accelerated growth and skeletal maturation and Tanner stage III breast and Tanner stage II pubic hair development at 7.3 years of age. This girl had growth hormone and corticotropin deficiencies, and a normal pubertal response of luteinizing hormone and follicle-stimulating hormone to luteinizing hormone–releasing hormone (LHRH). The second girl had a history of menarche at 10 years of age despite growth hormone and corticotropin deficiency. Our patient (patient 1) with septo-optic dysplasia and precocious puberty was described earlier as an example of precocious puberty associated with hypopituitarism. Although there are now reports on several large groups of patients with optic nerve hypoplasia and pituitary deficiency, little attention has been given to the patterns of puberty in these children. Costin and Murphree's[5] group of patients included only two teenagers 16 and 19 years of age, and no information about puberty was given. Margalith et al[8] measured luteinizing hormone and follicle-stimulating hormone response to LHRH in children with septo-optic dysplasia. One patient, a 6-year-old girl, had clinical precocious puberty and an "exaggerated response to LHRH." One 23-year-old man with a bone age of 14.5 years and one 15-year-old girl with a bone age of 11.5 years had

blunted responses to LHRH and were sexually infantile.

Our report shows that a large proportion of children with septo-optic dysplasia demonstrate abnormal puberty. Nearly half of our patients had an exceptional pattern of pubertal changes characterized by puberty at an early bone age, accelerated growth and skeletal maturation, and rapid sexual maturation. Since our study was retrospective, with many patients in their late teens or older at the time of review, consistent basal gonadotropin measurements or LHRH stimulation test results at the onset of puberty were not available. Nevertheless, the clinical and hormonal information that was available clearly indicates that this early, rapid puberty was due to hypothalamic-pituitary abnormalities. This pattern affected boys and girls, was most often associated with isolated growth hormone deficiency, and was independent of visual limitation. With the rapid advance in bone age these children lost substantial growth potential.

Some children with septo-optic dysplasia and documented growth hormone deficiency grow normally. This may be due to the effects of early production of sex steroids in the latter part of the first decade. Careful attention to changes in bone age in patients with septo-optic dysplasia may allow determination of which children are likely to have early and rapid pubertal development. In such children, a growth rate that is normal for age may not keep up with the advance in bone age associated with exceptionally rapid puberty. Despite a seemingly normal growth rate, growth hormone treatment should be given so as to maximize the growth response. Use of LHRH hormone agonists to slow or stop early puberty may be another option to preserve growth potential. If unrecognized, this common pattern of exceptional pubertal development will compromise final adult stature.

We thank Rosemary Allen for assistance in preparation of the manuscript.

References

1. Hoyt WF, Kaplan SL, Grumbach MM, et al: Septo-optic dysplasia and pituitary dwarfism. *Lancet* 1970;1:893-894.
2. Huseman CA, Kelch RP, Hopwood NJ, et al: Sexual precocity in association with septo-optic dysplasia and hypothalamic hypopituitarism. *J Pediatr* 1978;92:748-753.
3. Margalith D, Jun Tze W, Jan JE: Congenital optic nerve hypoplasia with hypothalamic-pituitary dysplasia. *AJDC* 1985;139:361-366.
4. LaFranchi SH: Sexual precocity with hypothalamic hypopituitarism. *AJDC* 1979;133:739-742.
5. Costin G, Murphree AL: Hypothalamic-pituitary function in children with optic nerve hypoplasia. *AJDC* 1985;139:249-254.
6. Greulich WW, Pyle SI: *Radiographic Atlas of Skeletal Development of the Hand and Wrist*, ed 2. Stanford, Calif, Stanford University Press, 1959.
7. Bayley N, Pinneau SR: Tables for predicting adult height from skeletal age: Revised for use with the Greulich-Pyle hand standards. *J Pediatr* 1952;40:423-441.
8. Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291-303.
9. Goodman HG, Grumbach MM, Kaplan SL: Growth and growth hormone: II. A comparison of isolated growth-hormone deficiency and multiple pituitary-hormone deficiencies in 35 patients with idiopathic hypopituitary dwarfism. *N Engl J Med* 1968;278:57-68.
10. Tanner JM, Whitehouse RH: A note on the bone age at which patients with true isolated growth hormone deficiency enter puberty. *J Clin Endocrinol Metab* 1975;41:788-790.

In Other AMA Journals

JAMA

Reduction in Motor Vehicle Fatalities Associated With an Increase in the Minimum Drinking Age
M. D. Decker; P. L. Graitcer; W. Schaffner (*JAMA* 1988;260:3604)

Evaluation of the Health Hazard of Clove Cigarettes
Council on Scientific Affairs (*JAMA* 1988;260:3641)

The Case for Safety Belt Use
D. Steed (*JAMA* 1988;260:3651)

The Onset of Sperm Production in Pubertal Boys

Relationship to Gonadotropin Excretion

Howard E. Kulin, MD; Miguel A. Frontera, MD; Laurence M. Demers, PhD; Mary J. Bartholomew, MS; Thomas A. Lloyd, PhD

• To determine the relationship of gonadotropin excretion to spermarche, 26 boys ranging in age from 10.3 to 17.5 years each provided ten overnight urine samples. Microscopic observation of sperm was found in 33 (13%) of the 260 samples, with 50% of the boys exhibiting sperm in at least one specimen. No further cumulative gain in detecting spermaturia occurred after the seventh urine collection. The median age of spermarche was computed by logistic regression analysis to be 14 years. Three urine collections from each boy were assessed for gonadotropin levels. At age 14 years mean follicule-stimulating hormone and luteinizing hormone excretion were, respectively, 857 and 503 mIU/h, into the reported adult daytime range. Spermarche is a midpubertal event associated with age-appropriate gonadotropin production.

(*AJDC* 1989;143:190-193)

The onset of reproductive potential in boys is not marked by an easily detectable event, as occurs with menarche in girls. The determination of the age at which the first release of spermatozoa takes place in boys (spermarche) has been hampered by social and ethical considerations regarding the request for semen samples. The appearance of sperm in urine (spermaturia), however, does provide useful information for studying the onset of reproductive potential in boys.

Early observations that sperm could be found in urine[1,2] sparked more recent interest in using urine samples as a sound approach for the determination of spermarche.[3-7] These later studies observed wide variability in the physical characteristics of individuals whose urine contained sperm[3,6,7] although a relatively early onset of sperm production in the course of the pubertal process was noted. Urinary testosterone and luteinizing hormone (LH) determinations were approximately midpubertal at the time of spermarche in the only investigation reporting hormone values.

Our study was designed to investigate the relationship of spermaturia to follicle-stimulating hormone (FSH) as well as LH production in pubertal boys, and to provide further data on the timing of onset of the process. In addition, small refinements in the methods for detecting sperm in urine were studied. Our results indicate that spermaturia is easy to detect in boys and does bear the expected relationship to increasing gonadotropin production.

SUBJECTS AND METHODS

Subjects and Urine Collections

The study group consisted of 26 boys ranging in age from 10.3 to 17.5 years recruited from a local school population. The study protocol was reviewed and approved by the Clinical Investigation Committee of the Pennsylvania State University College of Medicine and the Milton S. Hershey School, Hershey, Penn; all subjects and appropriate staff provided informed consent. Each boy was instructed to collect his first morning void in a standard urine container for two proximate periods of five consecutive days. Each of the ten urine samples was refrigerated at 4°C within two hours of voiding.

A history regarding masturbatory activity or sexual behavior was not obtained. Each boy was given a full physical examination, which included staging pubic hair and genitalia.[8] In addition, direct measurements of testicular length and phallic size were used to allow categories previously devised to provide a smooth continuum of secondary sex characteristic changes of puberty[9] as follows: stage 1 (prepuberty), testis less than 2.5 cm in length; stage 2 (early puberty), testis 2.5 to 2.9 cm, inclusive; stage 3 (midpuberty), testis 3.0 to 3.4 cm, penis more than 6.5 cm or pubic hair stage 2; stage 4 (late puberty), testis more than 3.4 cm, penis more than 8 cm or pubic hair stage 3; and stage 5 (adult), testis more than 3.9 cm, penis more than 11 cm and pubic hair stage 4.

Detection of Spermaturia

Each urine sample was prepared for microscopic examination within six to eight hours of voiding. In six urine samples that contained sperm, repeated examinations were performed daily between one to eight days after collection. While sperm were consistently observed over time in the six specimens, increasing amounts of urine sediment made sperm identification difficult after day 4 to 5.

Two 40-mL aliquots of each urine sample were centrifuged at 2000 rpm for 20 minutes. The supernatant was decanted and the sediment of one sample inspected for sperm. The sediment portions of each tube were then combined and the resultant material was also examined for sperm. In all 33 instances of spermaturia (of 260 urine samples collected), sperm were detected in a single 40-mL urine aliquot with the same frequency as that of combining the sediment from two samples of similar amounts (ie, 80 mL total).

The urine sediment was examined four times by placing a drop of material in a Makler chamber[10] and then scanning under the light microscope. Results were recorded as samples containing no sperm, one to 99 sperm, or more than 100 sperm per chamber field. Because of the unknown volume of centrifuged sediment, the exact quantitation of sperm per urine sample could not be calculated. While the mean age of nine boys who excreted at least one sample with more than 100 sperm per chamber field was higher than the four boys who excreted less than 100 sperm per chamber field (15.7 vs 14.3 years),

Accepted for publication Nov 9, 1988.

From the Department of Pediatrics, Division of Pediatric Endocrinology (Drs Kulin and Frontera), Department of Pathology, Core Endocrine Laboratory (Dr Demers), the Center for Biostatistics and Epidemiology (Ms Bartholomew), and the Department of Obstetrics/Gynecology, Division of Reproductive Endocrinology (Dr Lloyd), Milton S. Hershey Medical Center, The Pennsylvania State University, Hershey.

Reprint requests to Department of Pediatrics, Division of Endocrinology, Milton S. Hershey Medical Center, PO Box 850, Hershey, PA 17033 (Dr Kulin).

the FSH excretion in both groups was nearly identical. Consequently, the data were analyzed only with respect to the presence or absence of sperm, irrespective of a number of samples for a given individual or the number of sperm in the sediment of a given sample. Sperm morphologic features and motility were grossly normal in all cases.

Measurement of Urinary Gonadotropin Levels

Levels of LH and FSH were measured by radioimmunoassay utilizing the second international reference preparation of human menopausal gonadotropin (second IRP-HMG) as the reference standard. Aliquots of three random urine samples from each individual were prepared as previously described by precipitation with acetone, centrifugation, and resuspension in radioimmunoassay buffer.[11,12] Collection times ranged from three to 12 hours with a calculated urine output of more than 20 mL/h in all specimens. Results of the three urine samples were averaged and expressed in terms of milli–international units of second IRP-HMG per hour of FSH or LH.

Statistics

Logistic regression[13] was used to model the increasing log odds of spermaturia with increasing age. Using the logistic regression equation, the predicted probabilities and 95% confidence limits about them were generated for ages in the patient range (10.3 to 17.5 years). Follicule-stimulating hormone and LH levels were modeled as simple linear functions of age and 95% confidence bands were derived for those regression lines as well. Both regression procedures were those supplied in the Statistical Analysis System (SAS Institute, Cary, NC).

RESULTS

Detection of Spermaturia

Utilizing small refinements in the published techniques for assessing sperm in urine,[3-7] sample preparation can be simplified. A single 40-mL aliquot of an overnight collection can be used with reliable microscopic inspection performed within a few days of submission. Urine sediment can easily be examined using the Makler chamber, and the recognition of a single sperm constitutes significant spermaturia.

Of the 260 samples collected, 33 (13%) contained sperm. Thirteen of the 26 individual boys in the study had sperm in their urine. Two of these 13 boys excreted sperm in four or five of their ten urine samples; the remaining boys with sperm in their urine excreted sperm in one to three of the overnight collections.

As shown in Table 1, multiple urine collections must be obtained with no gain achieved after the seventh sample in this population. After the fifth sample, the cumulative increment in boys with sperm in their urine was a change from 35% to 50% between samples 5 and 7. Table 2 shows the increasing number of individuals who were found to excrete sperm with progression of age and pubertal stage; at age 16 to 17 years, six (86%) of seven boys had sperm in their urine.

Age of Spermarche

Despite a relatively small number of subjects studied, the boys were fairly well distributed across the peripubertal age range, as shown in Table 2. For pubertal staging by the criteria used, which employed testis size, some skewing toward later maturational stages is apparent (Table 2). If only a mean of the pubic hair and genital stages of Tanner[8] is employed, 14 boys were in stages 4 to 5 with 12 in stages 1 to 3.

The median age of spermarche was computed by logistic regression analysis and found to be 14 years. Ninety-five percent confidence bands about the predicted probabilities intersected the median at 12 and 16.2 years (Fig 1).

Gonadotropin Relationships

Based on nighttime—presumably sleep-entrained—gonadotropin excretion, the FSH and LH values for age 14 years and the computed median age of spermarche were well into the late pubertal age range (Table 2, Fig 2). At age 14 years, FSH excretion was predicted by linear regression to be 857 mIU/h and LH excretion was predicted to be 503 mIU/h.

COMMENT

Data on spermaturia in an American population have not, to our knowledge,

Table 1.—Appearance of Spermaturia in the Course of Ten Sequential Urine Collections in 26 Peripubertal Boys

	Sample Order									
Urine Collection	1	2	3	4	5	6	7	8	9	10
No. of new individuals with sperm in their urine	5	2	0	1	1	3	1	0	0	0
% of new individuals with sperm in their urine	19	10	0	5	6	18	7	0	0	0
Cumulative % of individuals with sperm in their urine	19	27	27	31	35	46	50	50	50	50

Table 2.—Nighttime Gonadotropin Excretion and Spermaturia in 26 Boys Grouped by Age and Pubertal Stage*

Group	Total No.	No. (%) Containing Sperm	FSH, mIU/h		LH, mIU/h	
			Mean	SEM	Mean	SEM
Age						
10-11	4	0 (0)	215	21	149	21
12-13	10	4 (40)	720	107	406	82
14-15	5	3 (60)	1150	230	655	94
16-17	7	6 (86)	1250	172	761	150
Pubertal stage						
1	2	0 (0)	180	. . .	151	. . .
2	5	0 (0)	325	38	177	20
3	2	1 (50)	656	. . .	280	. . .
4	8	5 (63)	1100	178	688	113
5	9	7 (78)	1160	125	668	104

*See "Subjects and Methods" section for pubertal staging criteria. FSH indicates follicle-stimulating hormone; LH, luteinizing hormone.

been reported. The median age of spermarche of 14 years ascertained in this small cross-sectional study is in agreement with the few investigations that have attempted to elucidate the onset of male reproductive functioning by examining urine for the presence of sperm. Richardson and Short's[3] initial estimate of 13.3 years in British school boys was confirmed in a longer, longitudinal protocol[6] in which the median age of spermarche was 13.8 years; in this later study, a correction factor of 0.41 years was used to allow for the frequency of samples negative for sperm and the sampling interval, providing a revised estimate of 13.4 years. Two Israeli studies[4,5] have also found spermarche to occur close to the 14th year of life, an age also consistent with the timing of the first conscious ejaculation.[14] While great variability in secondary sex characteristics was noted by Hirsch et al[5] and Nielsen et al,[6] boys were in midpubertal stages of sexual maturity based on pubic hair, testes size, and evidence of the growth spurt.

The origin of sperm in urine remains unclear, although prevailing evidence[15] suggests urethral washing after ejaculation to be the cause. Early observations that spontaneous urethral migration of sperm may occur[2] have not been substantiated, and no data are available bearing on such an occurrence in the pubertal male. Studies relating to masturbation behavior or nocturnal emis-

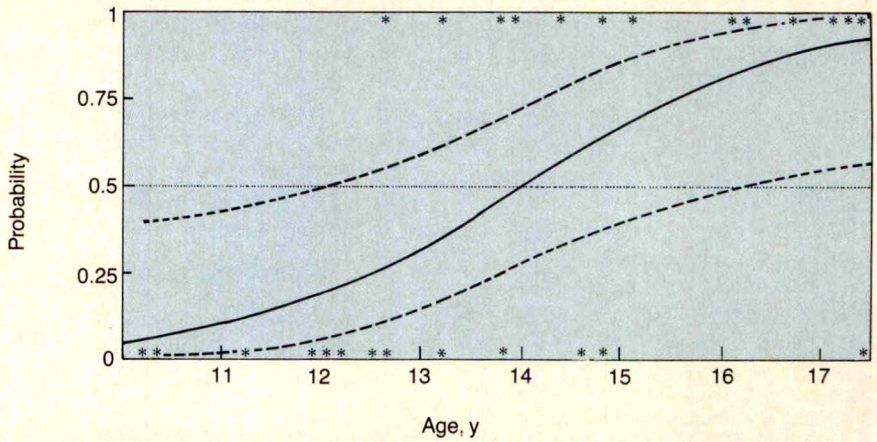


Fig 1.—Predicted probabilities (mean and 95% confidence intervals) of spermaturia by age. Median age at which 50% of individuals had sperm in their urine is 14 years. Asterisk at 1 on ordinate designates boy whose urine contained sperm; subject whose urine did not contain sperm is indicated by an asterisk at 0 on ordinate.

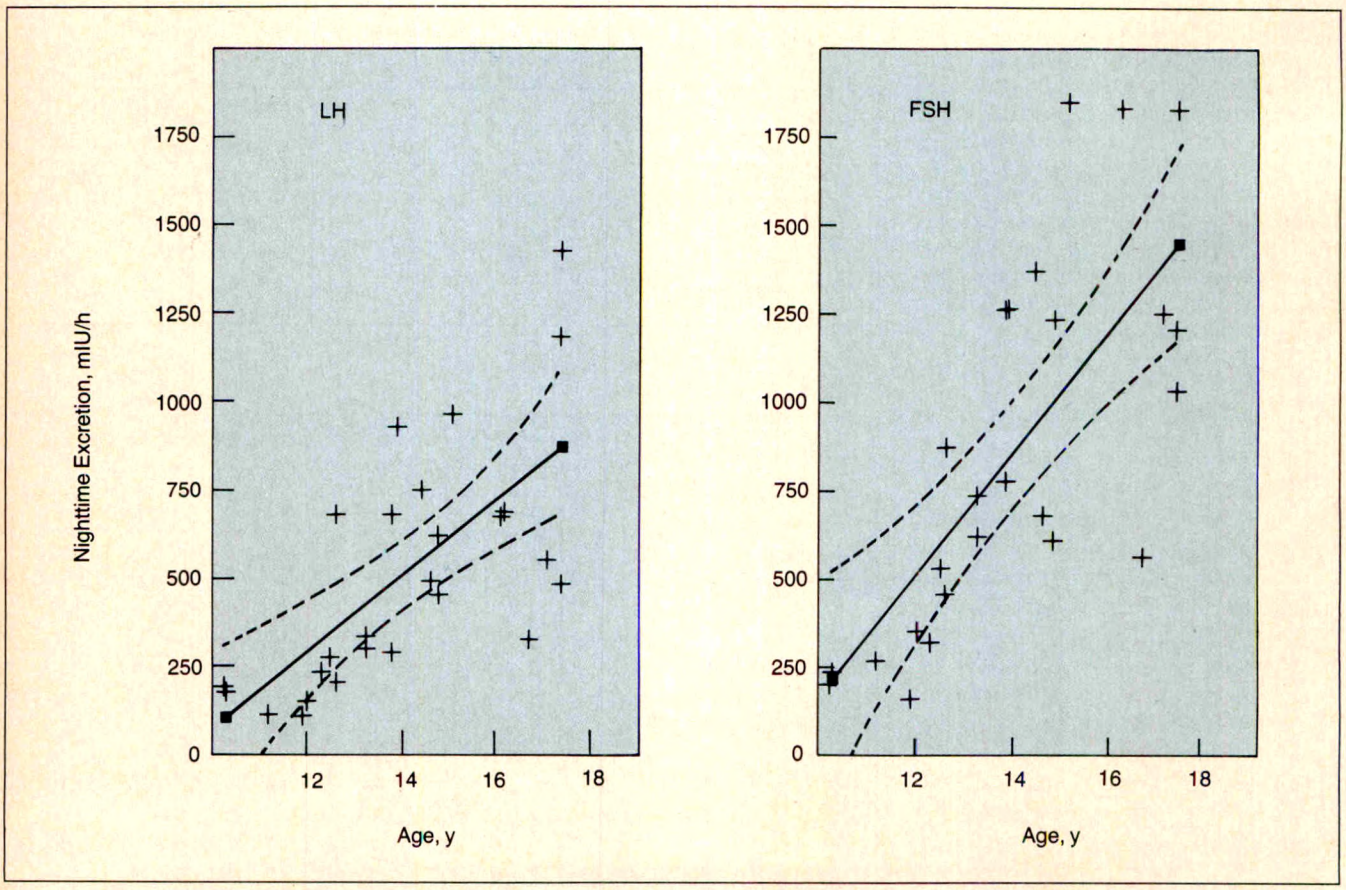


Fig 2.—Nighttime luteinizing hormone (LH) (left) and follicule-stimulating hormone (FSH) (right) excretion vs age in 26 peripubertal boys. Mean and 95% confidence limits are shown.

sions and spermaturia are not available. Caution must, therefore, be exercised in equating the appearance of spermaturia with spermarche.

Urinary testosterone has been studied in relation to spermarche[7] and midpubertal levels of steroid excretion are associated with the event. There are few gonadotropin data available on spermarche, with one study[7] indicating that late pubertal amounts of LH are associated with the phenomenon. The current LH values are in agreement with these findings and further reveal that considerable amounts of FSH are also produced in boys who excrete sperm in their urine.

The nighttime FSH value of 857 mIU/h at the median age of spermarche was, in fact, higher than the previously reported mean adult daytime value of approximately 500 mIU/h.[12] In this regard there remains sparse information bearing on circadian change in FSH during sexual maturation. By midpuberty, however, clearly adequate levels of gonadotropin and testosterone are available to sustain spermatogenesis.

Despite the paucity of studies bearing on spermarche, there is little doubt that sperm are easily identifiable in urine samples obtained from pubertal boys. The procedures used for observing sperm in urine have varied considerably, however, including sediment concentration, slide preparation, and staining of material before microscopic inspection. The use of the Mackler chamber in our study allowed for easy microscopic detection in a given sample. We found no gonadotropin difference whether a single sperm or more than 100 were observed in the whole grid field.

All studies of spermaturia agree on the intermittent nature of the phenomenon. In our investigation of pubertal boys, only 13% of all the specimens contained sperm; in Richardson and Short's investigation[3] of 484 samples from 134 boys aged 10 to 15 years, 18% had sperm in their urine. Although with increasing age more individuals excrete sperm (Table 2), a relatively large number of urine samples must be viewed (Table 1) to assure the presence or absence of spermaturia in a given subject. In the current study, there was no improved detection gained after the seventh specimen; Hirsch et al[5] found only a small cumulative increase (61% to 69%) in positive samples between the sixth and tenth specimens collected.

In summary, sperm can be easily detected in the urine of pubertal boys but multiple samples must be examined to observe spermaturia. In this small, cross-sectional study, spermarche was inferred at approximately age 14 years, an age when nighttime FSH levels were well into the adult male range.

The authors thank the participating students and administration of the Milton S. Hershey School for assistance in this work. Gonadotropin determinations were performed in the Core Endocrine laboratory of the Milton S. Hershey Medical Center. The manuscript was typed by Marlene Thompson.

References

1. Baldwin BT: The determination of sex maturation in boys by a laboratory method. *J Comp Psychol* 1928;8:39-42.
2. Wilhelm SF, Seligmann AW: Spermatozoa in urine. *Am J Surg* 1937;35:572-574.
3. Richardson DW, Short RV: Time of onset of sperm production in boys. *J Biosoc Sci Suppl* 1978;5:15-25.
4. Hirsch M, Shemesh J, Modan M, et al: Emission of spermatozoa, age of onset. *Int J Androl* 1979;2:289-298.
5. Hirsch M, Lunenfeld B, Modan M, et al: Spermarche: The onset of sperm emission. *J Adolesc Health Care* 1985;6:35-39.
6. Nielsen CT, Skakkebaek NE, Richardson DW, et al: The onset of release of spermatozoa in boys in relation to age, testicular growth, pubic hair, and height. *J Clin Endocrinol Metab* 1986;62:532-535.
7. Nielsen CT, Skakkebaek NE, Darling JAB, et al: Longitudinal study of testosterone and luteinizing hormone (LH) in relation to spermarche, pubic hair, height and sitting height in normal boys. *Acta Endocrinol* 1986;113(suppl):98-196.
8. Marshall MD, Tanner JM: Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13-23.
9. Kulin HE, Bwibo N, Mutie D, et al: The effect of chronic childhood malnutrition on pubertal growth and development. *Am J Clin Nutr* 1982;36:527-536.
10. Makler A: A new chamber for rapid sperm count and motility evaluation. *Fertil Steril* 1978;30:313-317.
11. Kulin HE, Bell P, Santen R, et al: Integration of pulsatile gonadotropin secretion by timed urinary measurements. *J Clin Endocrinol Metab* 1975;40:783-789.
12. Kulin HE, Santner SJ: Timed urinary gonadotropin measurements in normal infants, children and adults and in patients with disorders of sexual maturation. *J Pediatr* 1977;90:760-765.
13. Afifi AA: *Computer Aided Multivariate Analysis*. Belmont, Calif, Lifetime Learning Publications, 1984.
14. Laron Z, Gurewitz R, Grunebanm M, et al: Age of first conscious ejaculation: A milestone in male puberty. *Helv Paediatr Acta* 1980;35:13-20.
15. Weissenberg R, Rozenman H, Hova M, et al: Diagnostic value of sperm in postejaculatory urine. *Int J Androl* 1984;7:142-148.

In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Tonic Upgaze in Infancy: A Report of Three Cases

James C. Ahn, MD; William F. Hoyt, MD; Creig S. Hoyt, MD (*Arch Ophthalmol* 1989;107:59-62)

Clinical Indicators of Intracranial Lesion on Computed Tomographic Scan in Children With Parietal Skull Fracture

William A. Bonadio, MD; Douglas S. Smith, MD; Sylvia Hillman, MD

• We conducted a review of 98 cases of pediatric traumatic parietal skull fracture in which computed tomographic (CT) scans of the head were obtained during a seven-year period. There were 69 instances of an associated intracranial lesion identified in 47 children, including parenchymal injury (23), epidural hematoma (17), subdural hematoma (11), cerebral edema (ten), and subarachnoid hemorrhage (eight). Compared with 51 other children with parietal skull fracture and normal CT scans, the clinical characteristics significantly associated with the presence of an intracranial lesion were symptoms of neurologic dysfunction (loss or altered level of consciousness and/or seizure activity), neurologic compromise on examination (altered level of consciousness and/or focal deficit), or complicated skull fracture (bilateral, diastatic, and/or depressed). Of the 47 children with an intracranial lesion on CT scan, 44 had at least one of these significant clinical characteristics (sensitivity, 93%; specificity, 50%; positive-predictive value, 62%; and negative-predictive value, 96%). Children who sustain traumatic parietal skull fracture commonly experience associated intracranial injury. Those with evidence of neurologic deficit or complicated skull fracture are at particularly high risk, and should receive cranial CT scan evaluation.

(*AJDC* 1989;143:194-196)

Head trauma is a common injury in childhood: approximately 95 000 children sustain traumatic head injuries each year in the United States.[1] When fracture of the skull results, it usually denotes that significant trauma has occurred, with the potential for serious sequelae. If the skull fracture involves the parietal bone, especially in the region of the course of the middle meningeal artery, epidural hematoma, with resultant injury to the brain, can occur.

To our knowledge, no previous study has assessed the specific incidence of complications that result from traumatic parietal skull fracture in children. The purpose of this study was to assess the rate of associated intracranial injury that accompanies traumatic parietal skull fracture and to determine whether clinical criteria have predictive value for the presence of computed tomographic (CT) evidence of intracranial injury.

PATIENTS AND METHODS

We performed a retrospective analysis of consecutive cases of pediatric traumatic head injury with fracture of the parietal bone that were evaluated at the Children's Hospital of Wisconsin, Milwaukee, from 1981 to 1988. The medical records were reviewed, and patients who had received cranial CT scan evaluation were studied. The patients were divided into two groups. Group 1 had an intracranial lesion on CT scan, and group 2 had no intracranial abnormalities on CT scan. A complicated skull fracture was one in which bilateral, diastatic, and/or depressed fracture occurred. Statistical analysis (χ^2) was performed to assess the significance of the difference in rates of various clinical characteristics that were described for each group. The positive- and negative-predictive values of various clinical characteristics for the presence of intracranial lesion on CT scan were calculated.

RESULTS

During the study period, a total of 134 cases of traumatic parietal skull fracture occurred, involving 94 boys and 40 girls. There were 47 patients in group 1 and 51 patients in group 2. The other 36 patients did not receive cranial CT scan evaluation; all were hospitalized and experienced an uncomplicated clinical course without delayed onset of clinical signs indicative of an intracranial pathologic process requiring further diagnostic evaluation. The following clinical characteristics were assessed in all patients at the time of initial evaluation in the emergency department: patient age, nature of traumatic event, symptoms (loss or altered level of consciousness, vomiting, and/or seizure activity), physical findings (level of consciousness and/or neurologic deficit), roentgenographic results, and outcome. A comparison of the clinical characteristics of the two groups is given in Table 1. All study patients were hospitalized.

In group 1, intracranial abnormalities on CT scan included 23 instances of parenchymal injury (cerebral contusion or hemorrhage), 17 instances of epidural hematoma, 11 instances of subdural hematoma, ten instances of cerebral edema, and eight instances of subarachnoid hemorrhage. Of 17 patients with epidural hematoma, 12 were older than 2 years of age; 14 had an altered level of consciousness, which was documented either by history (reported by a witness at the scene) or at the time of initial examination. Of 11 patients with subdural hematoma, five were older than 1 year of age. Neurosurgical intervention was received by 11 of the 47 patients, including evacuation of epidural hematoma in eight patients and elevation of a depressed bone fragment of the skull in five patients. Forty-three patients survived and four patients died. In group 2, neurosurgical intervention included elevation of a depressed bone fragment of the skull in five patients; all patients survived.

Statistical analysis revealed that the clinical characteristics of patient age, traumatic event, and symptom of vomiting were not significantly associated with either group ($P>.1$). The statistical significance and predictive values of other clinical characteristics for the

Accepted for publication Oct 24, 1988.

From the Department of Pediatrics, The Medical College of Wisconsin, Children's Hospital of Wisconsin, Milwaukee.

Reprint requests to Department of Pediatrics, MS 756, Children's Hospital of Wisconsin, 1700 W Wisconsin Ave, Milwaukee, WI 53233 (Dr Bonadio).

Table 1.—Clinical Characteristics of Children With Parietal Skull Fracture

Parameter	No. of Patients	
	Group 1	Group 2
Age		
0-1 mo	3	3
1-12 mo	17	29
1-5 y	13	10
>5 y	14	9
Traumatic event		
Fall		
Caretaker's arms	1	11
Stairs	3	13
Second-story height	7	2
Chair/bed/table	10	10
Struck by missile	6	5
Motor vehicle–pedestrian collision	10	5
Motor vehicle–passenger accident	4	3
Physical abuse	6	2
Symptoms		
Loss of consciousness	21	8
Altered level of consciousness	19	4
Vomiting	13	8
Seizure activity	13	2
Physical findings		
Altered level of consciousness	32	6
Focal neurologic deficit	12	5
Roentgenographic results		
Parietal skull fracture		
Bilateral	6	4
Diastatic	9	4
Depressed	13	4

Table 2.—High-Yield Findings: Intracranial Lesion on Computed Tomographic Scan

Parameter	Yield, *P* Value	Predictive Value	
		Positive	Negative
Symptoms			
Loss of consciousness	<.01	.690	.623
Altered level of consciousness	<.001	.760	.631
Seizure activity	<.02	.786	.579
Any*	<.001	.692	.816
Physical findings			
Focal neurologic deficit	<.005	.778	.597
Altered level of consciousness	<.001	.811	.755
Any†	<.001	.806	.796
Roentgenographic results			
Complicated fracture	<.025	.629	.619

*Loss of consciousness, altered level of consciousness, or seizure activity.
†Altered level of consciousness or focal neurologic deficit.

presence of intracranial lesion are given in Table 2. In all, 44 of the 47 patients in group 1 exhibited at least one of the significant characteristics ($P<.001$; sensitivity, 93%; specificity, 50%; positive-predictive value, 62%; and negative-predictive value, 96%). Of three patients in group 1 without any of the significant characteristics identified, two were under 6 weeks of age (both were reported to be "more sleepy" than usual by their caretaker after head trauma), and one was the victim of physical abuse who sustained head trauma eight days prior to evaluation. In group 2, 24 of the 51 patients did not exhibit any of the significant characteristics.

COMMENT

Head trauma is a common pediatric injury, resulting from a multitude of accidents in all age groups. Up to 50% of children who sustain fracture of the skull have involvement of the parietal bone.[2] This type of head injury is of particular concern to the physician because of the potential for associated intracranial (epidural) hematoma, the signs and symptoms of which may not be initially apparent. Since a delay in surgical intervention for intracranial hematoma is associated with increased morbidity and mortality,[3] high-yield criteria predictive of the presence of this and other intracranial lesions would have merit. Several investigators[4,5] have previously evaluated the utility of clinical criteria for predicting intracranial abnormality on CT scan in children who sustained all types of traumatic head injury. Because of the heterogeneous nature of head trauma, their findings may not be representative of particular types of head injury.

The patient population in our study consisted of a large, diversely aged and traumatized group of children evaluated over a seven-year period. Our analysis was standardized, in that the same clinical characteristics were assessed in each patient. Overall, a high rate of serious morbidity was associated with head trauma accompanied by parietal skull fracture: approximately one third of those who received CT scan evaluation had intracranial injury, and one fourth of those with an identified lesion required neurosurgical intervention.

Previous investigations[4,5] did not find predictive value in the presence of neurologic deficit for CT scan abnormalities in children with head trauma. By contrast, we found that the presence of neurologic deficit, documented by history or on physical examination, was very sensitive in identifying those with parietal skull fracture accompanied by intracranial injury. In accord with the findings of Rivara et al[4] and as opposed to the findings of Mills et al[6], the presence of an altered level of consciousness

accurately distinguished those with from those without an intracranial lesion. Specifically, the presence of this finding on examination was six times more likely in those with an intracranial lesion. In 90% of those with epidural hematoma, this abnormality was reported on history or exhibited on examination. In accord with the findings of Mills et al[6] and as opposed to the findings of Rivara et al,[4] we found that seizure activity was significantly associated with the presence of an intracranial lesion. To our knowledge, no previous study has correlated the morphological characteristics of fracture of the skull with CT scan results in children with head trauma. We found that complicated fracture, perhaps indicative of high-impact injury, significantly correlated with the presence of intracranial injury. By contrast, only 4% of all children with parietal skull fracture and an intracranial lesion on CT scan were not characterized by any of the significant clinical criteria. Excluding the two neonates (in whom difficulty grading neurologic status might be expected), the presence of at least one of these criteria accurately predicted all children with *acute* injury. On the other hand, almost 50% of those with parietal skull fracture and a normal CT scan exhibited no neurologic abnormalities, and, as in previous studies,[7,8] fractures were usually of the linear, uncomplicated type. Thus, the presence of these criteria did not accurately distinguish those with a normal CT scan.

The variety of associated intracranial lesions observed in patients with parietal skull fracture is similar to those associated with other forms of head trauma. In contrast to the findings of previous studies[2,9] of children with all types of skull fracture, we found the incidence of epidural and subdural hematoma accompanying parietal skull fracture to be 10% (as opposed to 1%) and 8% (as opposed to 3%), respectively. Also, a majority (71%) of children with parietal skull fracture and epidural hematoma were older than 2 years of age, whereas subdural hematoma occurred with almost equal frequency in children both older and younger than 1 year of age.

In conclusion, children with posttraumatic parietal skull fracture are at significant risk for accompanying intracranial injury. We recommend that all children with head trauma involving the parietal area of the skull receive thorough clinical evaluation to assess neurologic status and roentgenographic evaluation to delineate the presence and character of possible fracture. Children with evidence of neurologic dysfunction or a complicated skull fracture should receive cranial CT scan evaluation. An associated intracranial lesion is rare in children with an uncomplicated, linear parietal skull fracture and no evidence of neurologic deficit. A high index of suspicion should be maintained for the presence of associated intracranial injury in infants who sustain parietal skull fracture, even in the presence of normal clinical findings.

References

1. Kraus JF, Fife D, Cox P, et al: Incidence, severity, and external causes of pediatric brain injury. *AJDC* 1986;140:687-693.
2. Hendrick E, Harwood-Hash D, Hudson A: Head injuries in children: A survey of 4465 consecutive cases at the Hospital for Sick Children, Toronto, Canada. *Clin Neurosurg* 1963;11:46-65.
3. Bricolo AP, Pasut LM: Extradural hematoma: Toward zero mortality. *Neurosurgery* 1984;14:8-12.
4. Rivara F, Tanaguchi D, Stimac GK, et al: Poor prediction of positive computed tomographic scans by clinical criteria in symptomatic pediatric head trauma. *Pediatrics* 1987;80:579-584.
5. Zimmerman RA, Bilaniuk LT: Computed tomography in pediatric head trauma. *J Neurosurg* 1981;8:257-271.
6. Mills ML, Russo LS, Vines FS, et al: High-yield criteria for urgent cranial computed tomographic scans. *Ann Emerg Med* 1986;15:1167-1172.
7. Narayan BK, Greenberg RP, Miller D, et al: Improved confidence of outcome prediction in severe head injury. *J Neurosurg* 1981;54:751-762.
8. Yarborough BE, Spillel J, Saunders CE: Lack of value of head CT scanning in alert, awake, neurologically intact victims of blunt trauma. *Ann Emerg Med* 1988;17:396.
9. Rosman NP, Herskowitz J, Carter AP, et al: Acute head trauma in infancy and childhood. *Pediatr Clin North Am* 1979;26:707-736.

In Other AMA Journals

ARCHIVES OF NEUROLOGY

The Spinal Accessory Nerve in Childhood Hemiplegia
Joseph C. Marcus, MB, BCh, FCP(SA) (*Arch Neurol* 1989;46:60-61)

Etiology and Mortality of Status Epilepticus in Children: A Recent Update
Steven A. Phillips, MD, Robin J. Shanahan, MD (*Arch Neurol* 1989;46:74-76)

Sports Medicine

William B. Strong, MD, Augusta, Ga
Carl L. Stanitski, MD, Pittsburgh
Ronald E. Smith, PhD, Seattle
Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*The quest for improved athletic performance by enhancement of physiologic measurements has become a major medical, sport, and ethical issue. Nonanemic, iron-deficient runners have the potential to improve performance after iron repletion. In the runners, the iron-deficient state was related to training, whereas in swimmers it is not related to training but to iron intake and menstrual blood loss. Optimization of iron stores has the potential for improving performance. In contrast to the nonphysiologic, pharmacologic responses of anabolic steroids, iron-replacement therapy is physiologic and medically indicated.*—W.B.S.

Iron Deficiency in Athletes

Insights From High School Swimmers

Thomas W. Rowland, MD, John F. Kelleher, MD

• Previous studies have indicated a high incidence of nonanemic iron deficiency in high school runners, but little is known regarding participants in other sports. The hematologic and iron status of 30 high school swimmers was assessed at the beginning and end of a competitive swim season. Iron depletion (serum ferritin level <12 μg/L) was initially present in 46.7% of the girls and none of the boys, yet among those subjects with hypoferritinemia there was no evidence of impaired red blood cell production. Serum haptoglobin levels were normal and did not correlate with serum ferritin levels. No significant change was observed in ferritin, hemoglobin, or haptoglobin concentrations during the course of the season. Dietary intake of iron was poor, particularly in the girls, in whom it averaged 43% of the recommended dietary allowance. Menstrual histories suggested an inverse relationship between the amount of menstrual flow and the serum ferritin level. These findings indicate a high prevalence of nonanemic iron deficiency in female high school swimmers that bears no relationship to swim training. Dietary inadequacies and menstrual blood flow appear to be important contributors to the hypoferritinemia observed in these athletes.
(*AJDC* 1989;143:197-200)

Iron deficiency in the absence of anemia is common in adolescent distance runners.[1-3] Depressed serum ferritin levels (<12 μg/L) with normal hemoglobin concentrations have been reported in 40% to 50% of female and 17% of male participants in high school cross-country running. The cause of hypoferritinemia in these athletes in unclear. Inadequate dietary iron intake, hemolysis, and losses through menstrual flow, sweat, urine, and stools have all been suggested as factors contributing to depressed iron stores.[4] Ferritin values decrease progressively during a competitive cross-country season, implying that the mechanism responsible for hypoferritinemia is linked to running training.[1,2,5]

Whether nonanemic iron deficiency affects athletic performance is unclear, as studies in animals and humans have produced conflicting results.[5-7] Considering the high prevalence of low ferritin levels in runners, reports suggesting that this condition diminishes running endurance bear particular importance for athletes and their coaches. Conversely, other data suggest that hypoferritinemia does not reflect a true state of iron deficiency. Magnusson et al[8] have contended that hemolysis incurred during running training causes iron to be sequestered in haptoglobin complexes rather than following the usual pathway to ferritin synthesis. If so, hypoferritinemia in runners is a "pseudodisease" of no consequence.

Few data are available regarding nonanemic iron deficiency in athletes other than runners. Assessment of iron status in non–weight-bearing sports in which

Accepted for publication Oct 25, 1988.
From the Department of Pediatrics, Baystate Medical Center, Springfield, Mass.
Reprint requests to Department of Pediatrics, Baystate Medical Center, 759 Chestnut St, Springfield, MA 01199 (Dr Rowland).

exercise-induced hemolysis is less likely should provide insights into the questions raised above. In the present study, competitive high school swimmers were evaluated during the course of a winter season to determine (1) the frequency and sex distribution of nonanemic iron deficiency; (2) the effect of ten weeks of intense swimming training on indicators of erythropoiesis, hemolysis, and iron stores; and (3) the contributions of hemolysis, diet, and menstrual blood loss to hypoferritinemia.

SUBJECTS AND METHODS

Thirty members of two high school swim teams volunteered for measurement of iron status and red blood cell production during a ten-week competitive season. The 15 male and 15 female subjects averaged 16.4 (SD = 0.8) years of age. All were in good health and reported no history of anemia. None was taking supplementary iron or other medications. Most were experienced swimmers, with an average of six prior seasons of participation on school or community teams (range, zero to ten years). Only two subjects had engaged in swim training in the three months immediately preceding the swimming season, but 13 played on fall sports teams (cross-country, soccer, gymnastics). Swim training consisted of 4000 to 5000 yards daily of combined speed and endurance events, five times weekly. Six subjects supplemented this regimen with either regular running or cycling.

At the beginning and end of the season blood specimens were obtained for measurement of levels of serum ferritin, hemoglobin, haptoglobin, and free erythrocyte protoporphyrin (FEP); red blood cell indexes (mean corpuscular volume [MCV], red blood cell distribution width [RDW]); and reticulocyte count. Specimens were drawn immediately before an afternoon practice session, at which time all subjects were free of acute febrile illness. Blood smears were examined by a board-certified pediatric hematologist (J.F.K.) for evidence of hemolysis.

At the first visit the girls completed a questionnaire seeking information regarding menstrual patterns. To estimate the amount of menstrual blood loss, a score was created by multiplying the number of pads or tampons used on the heaviest flow day by the number of days of menses. Dietary iron intake was assessed by a three-day prospective food diary (two days during the week and one weekend day). Instruction on weighing and measuring portion sizes was provided by a registered dietitian using food models. Total and available dietary iron were computed using standard reference sources,[9] and values were compared with a recommended dietary allowance (RDA) of 1.8 mg of available iron in both sexes.[10]

Blood cell counts were determined with an automated counter using standard methods. Anemia was defined by a hemoglobin concentration of less than 120 g/L in girls and less than 130 g/L in boys. The serum ferritin level was determined by enzyme immunoassay (Abbott Diagnostics, Highland Park, Ill). Iron depletion was considered indicated by values less than 12 μg/L. Free erythrocyte protoporphyrin levels were established by hemofluorometry (normal, 0 to 60 μg/dL) and the reticulocyte count was determined by standard manual methods (normal, <1.5%). Serum haptoglobin levels were assessed by the nephlometric technique (Beckman, Somerset, NJ) with a normal range of 0.22 to 1.95 g/L.

This study was approved by the research review committees of the Baystate Medical Center, Springfield, Mass. Informed written permission was obtained from the parents of all subjects. Pearson correlation coefficients were used to describe the relationship of ferritin levels with menstrual blood loss, haptoglobin, and hemoglobin values; male-female differences and preseason and postseason values were analyzed by unpaired and paired Student's t test, respectively. Significance was defined as $P<.05$.

RESULTS

At the beginning of the season only one subject was anemic (a boy with a hemoglobin level of 128 g/L and a ferritin level of 20 μg/L). The RDW, MCV, and FEP level were normal in all subjects (Table 1). Among the girls, seven (46.7%) of 15 demonstrated an initial serum ferritin level less than 12 μg/L, while iron deficiency was evident in none of the boys. Mean ferritin levels were significantly lower in the girls as well. Haptoglobin levels were within the normal range in both sexes. Seven of the boys and two of the girls had marginally elevated reticulocyte counts (only two over 2.5%), but review of blood smears failed to disclose evidence of increased polychromasia in any case. No correlation was observed between the serum ferritin level and haptoglobin, FEP level, or hemoglobin concentrations.

Two girls and one boy did not complete the season and were excluded from further data analysis, as were three girls with low ferritin levels who were subsequently treated with oral iron. Comparisons of preseason and postseason determinations for the remaining subjects are outlined in Table 2. No significant differences were observed for any of the criteria except an unexplained decline in FEP level in the boys and increased RDW and FEP level in the girls.

All but one girl experienced regular periods during training. The mean age of menarche was 12.9 years (SD = 1.0; range = 10.0 to 14.5). The average cycle was 28.8 days (SD = 3.1 days; range = 24 to 90 days) and the average duration of menstrual flow was 5.2 days (SD = 1.3 days; range = three to eight days). The girls reported an average of 4.9 changes of pads or tampons during the heaviest flow days (SD = 1.4 days; range = three to eight days). A correlation between the number of pads used on the heaviest flow day and the number of days of menstrual flow ($r=.45$; $P=.05$) supported the use of the menstrual score as an estimate of menstrual blood loss. An inverse relationship was observed between the menstrual score and initial ferritin level that barely escaped statistical significance ($r=-.50$; $P=.07$) (Figure).

Dietary iron information was obtained on six of the girls and nine of the boys. The average daily available iron

Table 1.—Mean Serum Values at Onset of Season*

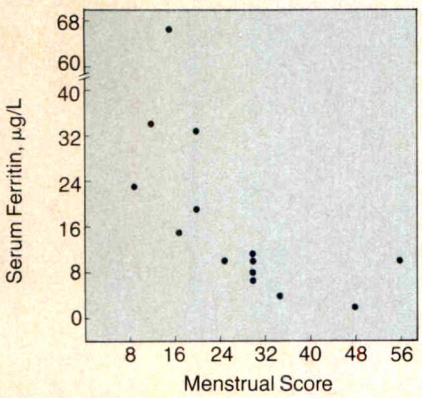
Measure	Boys (N = 15)	Girls (N = 15)
Hemoglobin, g/L	153 (10)	133 (05)†
Red blood cell distribution width, %	12.6 (0.5)	12.6 (0.8)
Mean corpuscular volume, μL³	89.1 (3.6)	88.9 (4.4)
Serum ferritin, μg/L	43.5 (19.0)	18.9 (15.8)†
Free erythrocyte protoporphyrin, μg/dL	23.2 (9.8)	22.4 (14.6)
Serum haptoglobin, g/L	0.58 (0.32)	0.73 (0.24)

*Values in parentheses are the SD.
†$P<.05$.

Table 2.—Mean Preseason and Postseason Values*

Measure	Boys (N = 14)		Girls (N = 10)	
	Week 0	Week 10	Week 0	Week 10
Hemoglobin, g/L	153 (9)	151 (11)	134 (6)	133 (8)
Red blood cell distribution width, %	12.6 (0.5)	12.7 (0.4)	12.4 (0.5)	12.9 (0.6)†
Mean corpuscular volume, μL^3	89.1 (3.7)	90.1 (4.7)	89.4 (4.8)	88.3 (3.9)
Serum ferritin, μg/L	44.8 (19.0)	45.1 (24.5)	21.5 (17.1)	20.2 (13.7)
Reticulocytes, %	1.8 (0.8)	1.6 (0.5)	1.5 (0.3)	1.6 (0.6)
Free erythrocyte protoporphyrin, μg/dL	23.4 (10.1)	11.9 (9.2)†	18.6 (11.2)	21.3 (13.3)†
Serum haptoglobin, g/L	0.54 (0.29)	0.57 (0.42)	0.69 (0.19)	0.70 (0.23)

*Values in parentheses are the SD.
†$P<.05$.



Serum ferritin levels at beginning of competitive swim season compared with menstrual score (see text for details).

intake was 0.78 mg (range, 0.5 to 1.5 mg) in the female swimmers, representing 43.3% of the RDA. Comparable values in the boys were 1.21 mg (range, 0.5 to 1.6 mg) and 67%. All subjects, regardless of sex, reported an iron consumption that was less than the RDA.

COMMENT

Previous evaluation of the hematologic status of distance runners has indicated that (1) nonanemic iron deficiency is common, (2) this condition occurs much more frequently in girls or women, and (3) serum ferritin levels fall during training, implying that the mechanism for hypoferritinemia is related to repetitive exercise.[1-5] Less is known regarding swimmers. Selby and Eichner[11] described serum ferritin levels below 15 μg/L in 11% of male and 57% of female adult trained swimmers. Seven (25%) of 27 swimmers had serum haptoglobin levels less than 0.03 g/L at the beginning of a competitive season. Selby and Eichner[11] suggested that this baseline hypohaptoglobinemia might be the result of chronic intravascular hemolysis; however, no reticulocytosis was observed. Conversely, in a group of adult male trained swimmers, Dickson et al[12] reported ferritin levels higher than in both runners and control subjects, and no swimmer had a ferritin level less than 30 μg/L. Pelliccia and DiNucci[13] also reported higher ferritin levels in competitive female swimmers compared with controls, but the possible influence of supplementary iron intake was not investigated.

In the present study almost one half of female high school swimmers demonstrated a ferritin level less than 12 μg/L at the beginning of the season, an incidence similar to that previously reported in adolescent runners.[1-3] Attention to nonanemic iron deficiency is therefore warranted in this group of athletes, since some data indicate that hypoferritinemia may impair exercise performance.[5] However, swimming training for ten weeks had no observable effect on hematologic or iron status, suggesting that this sport does not, per se, lead to iron deficiency in high school athletes.

Why did the girl swimmers in this study demonstrate low preseason ferritin levels? The observation in previous reports that iron deficiency is consistently greater in female subjects has implied a substantial contribution by menstrual iron loss. In support of this conclusion, the present investigation suggested that menstrual flow was greater in those girls with lower ferritin levels. A lack of dietary iron is potentially an important factor in hypoferritinemia as well. In the six girls studied, not one reported iron intake that exceeded 60% of the RDA. Dietary iron intake in the male swimmers was 50% higher than in the girls, although still less than the RDA in all cases. These findings are similar to those in previous reports.[2,14,15]

Are these subjects with low serum ferritin levels truly iron deficient? Suspicion concerning this issue is raised by the fact that no impairment of erythropoiesis was observed by several sensitive markers of hemoglobin formation (FEP level, RDW, MCV). This was evident even with ferritin levels as low as 4 to 8 μg/L, values that are typically observed with overt iron deficiency anemia in other clinical settings. On the other hand, the fact that hypoferritinemia was limited to girls and is consistent with menstrual losses and lower dietary iron intake supports the concept that these individuals were low in body iron stores.

Data in competitive runners indicate that low ferritin levels are related to training, since (1) values are less than in untrained individuals[16,17] and (2) ferritin concentrations progressively decrease during a competitive season.[1,2,5] Hemolysis of red blood cells, possibly due to the mechanical trauma to the capillaries of the feet, has been offered as a possible explanation, and this is supported by findings of decreased haptoglobin values in groups of runners with low ferritin levels.[8,14] Rises in the bilirubin level and reticulocyte count after a competitive race have also been cited as evidence of acute hemolysis accompanying running.[18] A more comprehensive hematologic evaluation of indicators of chronic hemolysis in runners is lacking,

however. In the runners studied by Martin et al,[19] only a small increase in reticulocyte count was observed. Steenkamp et al[20] could find no evidence to indicate hemolysis by changes in red blood cell survival, bilirubin levels, haptoglobin concentration, or direct blood smear observation in iron-replete women either during training for a marathon race or immediately afterward.

In the present study, no evidence of major hemolysis was evident by reticulocyte count, haptoglobin level, or blood smear.

The results indicate that swimming training did not lead to red blood cell breakdown in this group of athletes, suggesting that hemolysis does not occur in athletes by compression of the muscles during physical activity.

The authors wish to express their appreciation to coaches Isabel Fraser and Richard Bolles and members of the Longmeadow (Mass) and East Longmeadow (Mass) High School swim teams for their cooperation in this study. Acknowledgement is also made to Nancy Bobskill, RD, for nutritional analysis and Marilyn Richards, RN, Marianne Cumming, and Barbara Sheldon for their invaluable assistance.

References

1. Rowland TW, Black SA, Kelleher JF: Iron deficiency in adolescent endurance athletes. *J Adolesc Health Care* 1987;8:322-326.

2. Nickerson HJ, Holubets M, Tripp AD, et al: Decreased iron stores in high school female runners. *AJDC* 1985;139:1115-1119.

3. Nickerson HG, Tripp AD: Iron deficiency in adolescent cross country runners. *Phys Sportsmed* 1983;11:60-66.

4. Clement DB, Sawchuck LL: Iron status and sports performance. *Sports Med* 1984;1:65-74.

5. Rowland TW, Deisroth MB, Green GM, et al: The effect of iron therapy on the exercise capacity of nonanemic iron-deficient adolescent runners. *AJDC* 1988;142:165-169.

6. Finch CA, Miller LR, Inamdar AR, et al: Iron deficiency in the rat: Physiological and biochemical studies of muscle dysfunction. *J Clin Invest* 1976;58:447-453.

7. Celsing F, Blomstrand E, Werner B, et al: Effects of iron deficiency on endurance and muscle enzyme activity in man. *Med Sci Sports Exerc* 1986;18:156-161.

8. Magnusson B, Hallberg L, Rossander L, et al: Iron metabolism and 'sports anemia': I. A study of several iron parameters in elite runners with difference in iron status. *Acta Med Scand* 1984;216:149-155.

9. Penington JAT, Church HN: *Food Values of Portions Commonly Used*, ed 14. Philadelphia, JB Lippincott, 1985.

10. *Recommended Dietary Allowances*, ed 9. Washington, DC, National Academy of Sciences, 1980.

11. Selby GB, Eichner ER: Endurance swimming, intravascular hemolysis, anemia, and iron depletion. *Am J Med* 1986;81:791-794.

12. Dickson DN, Wilkinson RL, Noakes TD: Effects of ultramarathon training and racing on hematologic parameters and serum ferritin levels in well-trained athletes. *Int J Sports Med* 1982;3:111-117.

13. Pelliccia A, DiNucci GB: Anemia in swimmers: Fact or fiction? Study of hematologic and iron status in male and female top-level swimmers. *Int J Sports Med* 1987;8:227-230.

14. Clement DB, Asmundson RC: Nutritional intake and hematologic parameters in endurance runners. *Phys Sportsmed* 1982;10:37-43.

15. Frederickson LA, Puhl JL, Runyan WS: Effect of training on indices of iron status of young female cross country runners. *Med Sci Sports Exerc* 1983;15:271-276.

16. Crowell DL, Crouse SF, Hooper PL, et al: Hematological parameters in endurance-trained and sedentary men, abstracted. *Med Sci Sports Exerc* 1985;17:293.

17. Pate RR, Baldwin C, Slentz C, et al: Iron status of female runners, abstracted. *Med Sci Sports Exerc* 1986;18: S55.

18. Dressendorfer RH, Askew EW, Rimar JE, et al: Development of sports anemia in men without iron deficiency, abstracted. *Med Sci Sports Exerc* 1985;17:201.

19. Martin DE, Vroon DH, May DF, et al: Physiological changes in elite male distance runners training for the Olympic games. *Phys Sportsmed* 1986;14:152-171.

20. Steenkamp I, Fuller C, Graves J, et al: Marathon running fails to influence RBC survival rates in iron-replete women. *Phys Sportsmed* 1986;14:89-95.

In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY

National Institutes of Health Consensus Development Conference Statement on Cochlear Implants

Consensus Development Panel (*Arch Otolaryngol Head Neck Surg* 1989;115:31-36)

A Word of Caution

Charles W. Cummings, MD (*Arch Otolaryngol Head Neck Surg* 1989;115:36)

Human Leukocyte Antigen in Childhood Unilateral Deafness

Kazumasa Matsuki, MD; Takehiko Harada, MD; Takeo Juji, MD; Jin Kanzaki, MD; Keijiro Koga, MD; Minoru Toriyama, MD (*Arch Otolaryngol Head Neck Surg* 1989; 115:46-47)

Treatment of the Young Child With Postoperative Central Diabetes Insipidus

Jay A. McDonald, MD; Paul M. Martha, Jr, MD; James Kerrigan, MD; William L. Clarke, MD; Alan D. Rogol, MD, PhD; Robert M. Blizzard, MD

• A continuous intravenous infusion of aqueous vasopressin (dosage range, 1.0 to 3.0 mU/kg/h) was administered to two patients (respective ages, 2 weeks and 3 years 1 month) who had postoperative central diabetes insipidus to determine if this mode of therapy is helpful in the very young patient. In both patients the polyuria and serum hyperosmolality were corrected. These findings suggest that an intravenous infusion of aqueous vasopressin can provide satisfactory control of the polyuria and electrolyte disturbances found in young children with acute postoperative central diabetes insipidus.

(*AJDC* 1989;143:201-204)

Central diabetes insipidus (CDI) is a frequent complication after intracranial surgery in the area of the hypothalamus and/or the posterior pituitary gland.[1,2] It is characterized by a loss of urinary concentrating capacity due to a relative antidiuretic hormone deficiency that results in polyuria, despite serum hyperosmolality and decreased intravascular volume.

Postoperative CDI may be transient or permanent and complete or partial, and presents either abruptly, with severe symptomatology, or insidiously, depending on the level and degree of hypothalamic damage.[3]

Postoperative management of fluid and electrolyte balance in the presence of acute CDI in the very young patient subjected to craniotomy is often difficult. Furthermore, increased intracranial pressure from cerebral edema, anterior pituitary hormone deficiencies, and the perioperative use of phenytoin sodium, dexamethasone sodium, and morphine sulfate, drugs that may affect ADH secretion and free water clearance, can complicate management.

Traditional treatment for acute CDI in neonates and young children has included the use of short- or long-acting antidiuretic hormone analogues.[4-7]

Herein we report the successful use of a continuous intravenous infusion of aqueous vasopressin (Pitressin) in the management of postoperative CDI in two very young patients.

PATIENT REPORTS

PATIENT 1.—A 3-day-old male infant was evaluated for macrocephaly and microphallus. He was born to an 18-year-old primiparous woman by cesarean delivery after a prenatal ultrasound examination that disclosed hydrocephalus. His estimated gestational age was 38 weeks.

He was a large, irritable neonate with a blood pressure of 92/50 mm Hg, heart rate of 122 beats per minute, and respiratory rate of 28/min. His weight was 3430 g (75th percentile), his length was 50.0 cm (50th percentile), and his head circumference was 38.0 cm (>95th percentile). The sagittal and coronal sutures were split with a tense anterior fontanelle measuring 9×7 cm; the eyes had a "sunsetting" appearance, and the patient had a micropenis (1.8 cm long) with bilaterally descended testes.

A cranial computed tomographic scan demonstrated a large, partially calcified, cystic mass in the suprasellar area and dilated lateral ventricles. Pertinent preoperative studies at 1 week of age included a serum sodium level of 138 mmol/L , serum osmolality of 279 nmol/kg, and urinary osmolality of 242 mmol/kg. Other laboratory data as well as results of preoperative endocrine studies are listed in Table 1. The patient received parenteral thyroid hormone replacement (levothyroxine sodium [Synthroid], 12 μg/d intramuscularly) for two days before surgery. The urinary output was 3.0 mL/kg/h during the two days before surgery with an appropriate oral intake of 100 to 130 mL/kg/d of standard formula. No episodes of hypoglycemia or electrolyte imbalance occurred before surgery.

The suprasellar mass, a craniopharyngioma, was resected in two stages one week apart. The patient was treated postoperatively with thyroid and glucocorticoid replacement in physiologic doses. The weight, urinary output, and serum electrolyte levels remained stable after the first surgical procedure. After the second surgical procedure (completion of gross total resection), the patient's weight, urinary output, and serum electrolyte levels remained stable for the first two days with intravenous fluid therapy of 100 to 125 mL/kg/d. Postoperative seizures were controlled with phenytoin sodium and phenobarbital sodium. Intravenous dexamethasone (1 mg/kg/d) was administered for cerebral edema. On the second postoperative day the urinary output was 2.0 to 3.0 mL/kg/h with a serum sodium level of 138 mmol/L, serum osmolality of 292 nmol/kg, and urinary osmolality of 492 mmol/kg. Approximately 60 hours after surgery the urinary output rose abruptly to 12 to 13 mL/kg/h without a change in the fluid therapy or diuretic administration. Laboratory studies performed at that time (Table 1) demonstrated serum hypernatremia and hyperosmolality with urinary hypoosmolality, confirming the impression of acute diabetes insipidus.

A constant intravenous infusion of aqueous vasopressin (Pitressin in a 5% dextrose solution) at a dose of 3.0 mU/kg/h was begun. Fluid therapy was continued at the same rate. As shown in Table 1, the polyuria was corrected within four hours of the vasopressin administration. The serum osmolality gradually declined and the urinary osmolality increased appropriately in response to the vasopressin. The following day mild hyponatremia developed and the infusion dosage was reduced to 1.5 mU/kg/h without recurrence of the polyuria. The vasopressin dosage was slowly decreased and administration was discontinued on the fifth postoperative day. At that time serum electrolyte levels were stable and remained so. At this writing the patient's CDI had not recurred. However, he did require ventriculoperitoneal shunt placement for obstructive hydrocephalus. He was treated with anterior pituitary hormone replacement and anticonvulsants. At 20 months of age his physical problems included global developmental delay, visual impairment, and a seizure disorder.

Accepted for publication Nov 17, 1988.

From the Department of Pediatrics, University of Virginia School of Medicine, Charlottesville.

Reprint requests to Division of Endocrinology, Department of Pediatrics, Box 386, University of Virginia School of Medicine, Charlottesville, VA 22908 (Dr McDonald).

Table 1.—Data on Patient 1

Characteristic	Preoperative Data	Diagnosis of Postoperative CDI*	Intravenous Vasopressin 4 h	Intravenous Vasopressin 12 h	Intravenous Vasopressin 24 h
Weight, kg	3.90	3.88	...	...	...
Urinary output, mL/kg/h	3.0	12.4	4.6	4.1	4.0
Serum					
Sodium, mmol/L	138	149	144	140	135
Osmolality, nmol/kg	279	315	312	304	290
Glucose, mmol/L	3.4	7.2	...	...	...
Urea nitrogen, mmol/L of urea	1.4	6.4	...	...	...
Creatinine, μmol/L	44.2	77.0	...	...	...
Morning cortisol, nmol/L	248	...	...	...	...
Thyroxine, nmol/L	61.8	...	...	...	...
Thyrotropin, mU/L	8	...	...	...	...
Urine					
Osmolality, mmol/kg	242	135	243	446	473
Sodium, mmol/L	38	11	82	134	68
Specific gravity	1.005	1.004	1.007	1.010	1.010

*CDI indicates central diabetes insipidus. The diagnosis was made 60 hours postoperatively.

PATIENT 2.—A 3-year-1-month-old girl had a six-month history of poor linear growth and the recent onset of left-sided strabismus and nystagmus. There was no history of headaches, seizures, or gait disturbance. She appeared healthy and was short (height, 86.0 cm; less than fifth percentile). Her weight was 13.1 kg (25th percentile) and her head circumference was 50.5 cm (80th percentile). Her blood pressure was 90/68 mm Hg, her heart rate was 92 beats per minute, and her respiratory rate was 18/min. She had an intermittent left-sided exotropia and torsional nystagmus, a left afferent pupillary defect, and a pale left optic disc. Uncorrected visual acuity in the right eye was 20/60. Visual acuity in the left eye was severely impaired, as she was only able to count fingers at 1 m.

A cranial computed tomographic scan and magnetic resonance imaging showed a large, 4-cm, cystic suprasellar mass with intrasellar extension. Results of preoperative studies are listed in Table 2. Pertinent values included a serum sodium level of 138 mmol/L and a morning urinary specific gravity of 1.025.

The patient underwent a complete gross surgical resection of a craniopharyngioma. A complete hypophysectomy was performed in addition to the suprasellar dissection because of the extension of the tumor. The patient was treated perioperatively with physiologic doses of adrenal and thyroid hormones. Polyuria was noted within two hours of hypophysectomy. As shown in Table 2, urinary output rose abruptly in the immediate postoperative period. Before the administration of vasopressin, laboratory studies disclosed serum hypernatremia and hyperosmolality with relative urinary hypo-osmolality consistent with the diagnosis of diabetes insipidus. Intravenous aqueous vasopressin (Pitressin diluted in 0.9% isotonic saline solution) was administered at a rate of 3.0 mU/kg/h. Within 60 minutes after the infusion had begun the urinary output decreased to 4 mL/kg/h. Follow-up laboratory data obtained 4, 24, and 36 hours after the beginning of the vasopressin infusion are shown in Table 2. There was a correction of the polyuria and the electrolyte disturbances. On the third postoperative day serum electrolyte concentrations and osmolality remained normal. The vasopressin infusion was gradually decreased and then discontinued but the polyuria returned. The patient was treated with 0.05 mL (5 μg) of desmopressin acetate intranasally every 12 hours. At this writing she continued to be treated twice daily with intranasal desmopressin. Two months after the craniotomy the patient was shown to have growth hormone deficiency. At 3 years 8 months of age the patient was receiving anterior and posterior pituitary hormone replacement. There was no recurrence of her craniopharyngioma.

COMMENT

Water homeostasis in humans is mainly controlled through changes in antidiuretic hormone secretion and thirst in response to changes in serum osmolality and, to a lesser extent, intravascular volume.[3] Antidiuretic hormone is released from the posterior pituitary gland and facilitates water reabsorption in the distal renal tubule and collecting duct, resulting in water retention and concentration of the urine. A deficiency in antidiuretic hormone results in CDI, a clinical condition characterized by the loss of urinary concentrating ability, resulting in polyuria despite serum hyperosmolality, and even hypovolemia.

Central diabetes insipidus is usually caused by acquired central nervous system (CNS) disease in the area of the hypothalamus and/or posterior pituitary gland. The severity and duration of the polyuria and concentrating defect depend on the location as well as the completeness of the CNS lesion affecting antidiuretic hormone secretion.[3] Lesions that involve the supraoptic and paraventricular hypothalamic nuclei, or interrupt the hypothalamic-neurohypophyseal tract above the level of the median eminence, are more likely to cause permanent CDI than are those within the sella turcica. Although there are multiple causes of CDI,[4-8] the most common cause is an intracranial tumor.[8] Patients with CDI associated with CNS tumors usually have their onset postoperatively because of regional brain swelling or disruption of the hypothalamic–posterior pituitary axis.[3,8] In children, the lesions most often associated with postoperative polyuria and impaired postoperative urinary concentrating ability include craniopharyngioma, dysgerminoma, and supraoptic glioma and astrocytoma.[2,3,8]

The difficulties in managing acute CDI in neonates, infants, and young children have been described previously.[4-6] These include wide fluctuations in serum osmolality, serum sodium concentration, and urinary output often en-

Table 2.—Data on Patient 2

Characteristic	Preoperative Data	Diagnosis of Postoperative CDI*	Intravenous Vasopressin 4 h	Intravenous Vasopressin 24 h	Intravenous Vasopressin 36 h
Weight, kg	13.1	13.2	...	...	...
Urinary output, mL/kg/h	2.0	18.5	3.5	2.8	2.3
Serum					
Sodium, mmol/L	138	149	144	139	142
Osmolality, nmol/kg	285†	310	300†	289	293
Glucose, mmol/L	4.5	8.3	...	...	...
Urea nitrogen, mmol/L of urea	12	6.4	...	...	...
Creatinine, μmol/L	44.2	97.2	...	44.2	...
Morning cortisol, nmol/L	138	...	...	...	...
Thyroxine, nmol/L	154.6	...	...	...	...
Thyrotropin, mU/L	2.1	...	...	...	...
Urine					
Osmolality, mmol/kg	...	98	218	605	705
Sodium, mmol/L	...	7	...	45	...
Specific gravity	1.025	1.003	1.005	1.015	1.020

*CDI indicates central diabetes insipidus. The diagnosis was made two hours postoperatively.
†Calculated using the following formula: (2 × sodium) + (glucose/18) + (serum urea nitrogen/2.8).[14]

countered with the use of long-acting forms of vasopressin such as Pitressin tannate in oil, and even intranasal or intravenous desmopressin, despite aggressive intravenous fluid therapy. In addition, in the immediate postoperative period these patients are often unable to respond to thirst.

There are limited data regarding the use of intravenous vasopressin in patients with CDI. Chanson et al[9] reported on a series of 12 patients (age range, 9 to 58 years) with acute CDI after craniotomy who were treated with low doses of intravenous vasopressin at a dosage of 1.6 ± 0.26 mU/kg/h, and Levitt et al[10] have reported the use of intravenous vasopressin in the management of acute posttraumatic CDI in an adult. Moreover, an intravenous aqueous vasopressin stimulation test has been used to evaluate a patient with familial CDI.[11] We were unable to find previous reports of the short-term use of a constant intravenous infusion of aqueous vasopressin in the management of CDI in a neonate, infant, or young child.

In both of the patients described above, CDI was anticipated because of the anatomic locations of the tumors. The decision to use an intravenous vasopressin infusion was made preoperatively. Although classic water-deprivation tests could not be performed, both patients met sufficient diagnostic criteria for acute CDI. Both patients experienced a sudden onset of polyuria and had persistent, inappropriately dilute urine despite serum hyperosmolality and hypernatremia that were corrected after the administration of vasopressin. In patient 1 the onset of CDI occurred approximately 60 hours after surgery. In patient 2 the CDI became apparent two hours postoperatively. The use of a continuous low-dose intravenous infusion of vasopressin permitted rapid titration of urinary output and adjustment of intravenous fluids in an optimal manner in both cases. Neither patient experienced systemic hypertension while receiving the vasopressin.

The diabetes insipidus in patient 1 may have been related to localized or generalized cerebral edema since the onset occurred approximately 60 hours after surgery and was transient. This suggests that there was a sufficient number of antidiuretic-hormone–synthesizing neurons in the hypothalamic nuclei to maintain normal water homeostasis once cerebral edema resolved. This patient did not have a recurrence of CDI.

On the other hand, patient 2 underwent total hypophysectomy as well as hypothalamic dissection for complete gross resection of a craniopharyngioma. At this writing the CDI had persisted and was believed to be permanent. The patient was receiving a stable dose of desmopressin along with anterior pituitary hormone replacements.

In the care of acute postoperative CDI in the young infant or child the following plan is recommended:

1. All patients undergoing craniotomy for neoplasms in the hypothalamic-pituitary area should undergo preoperative evaluation of urinary concentrating ability as well as anterior pituitary gland function.

2. The clinical and laboratory condition of CDI should be allowed to develop postoperatively before initiating treatment to be certain of the diagnosis. Other possible causes of polyuria (hyperglycemia, overhydration, diuretic administration) should be ruled out.

3. The patient should not receive any fluids orally during the immediate postoperative period. Intravenous fluids may be given at a physiologic maintenance rate[12] (or less if indicated). Fluid deficits may be corrected after the initiation of vasopressin infusion. Strict hourly observation of fluid intake and output and blood pressure is essential. Frequent monitoring of serum and urinary osmolalities, serum and urinary sodium concentrations, and other serum electrolyte levels should be performed before and after the vasopressin infusion is started.

4. Vasopressin infusion (aqueous vasopressin in a 5% dextrose and water solution or 0.9% isotonic saline solution) should be started at a dosage of 1.5 mU/kg/h (0.025 mU/kg/min) and increased if necessary to control urine output. The dose range used in our patients was 1.0 to 3.0 mU/kg/h. It is preferable to administer the vasopressin via a constant-infusion pump.

5. The infusion can be used several days if necessary. If CDI persists, intranasal administration of desmopressin may be started when the patient's fluid and electrolyte status is stable. The half-life of antidiuretic hormone in circulation is less than 30 minutes.[13] Therefore, desmopressin should be given shortly after discontinuation of the intravenous vasopressin infusion.

In summary, CDI often complicates the postooperative care of the patient who has undergone craniotomy. Short-term management of this dynamic complication may be difficult. The goal of therapy should be to maintain stable fluid and electrolyte balance through consistent antidiuresis. The use of a continuous, low-dose intravenous vasopressin infusion allows hour-to-hour control and stabilization of urine output. This form of therapy should be used in the intensive care setting where continuous monitoring of systemic blood pressure, urinary output, serum electrolyte levels, and osmolality can be performed. Constant intravenous vasopressin infusion should also be considered in the management of other acute CDI conditions, such as those associated with head injury, and in patients who are brain dead and are being considered for organ donation.

References

1. Shucart WA, Jackson I: Management of diabetes insipidus in neurosurgical patients. *J Neurosurg* 1976;44:65-71.
2. Czernichow P, Pomarede R, Brauner R, et al: Neurogenic diabetes insipidus in children. *Front Hormone Res* 1985;13:190-209.
3. Bode HH: Disorders of the posterior pituitary, in Kaplan SA (ed): *Clinical Pediatric and Adolescent Endocrinology*. Philadelphia, WB Saunders Co, 1982, pp 49-69.
4. Pai KG, Rubin HM, Wedemeyer PP, et al: Hypothalamic-pituitary dysfunction following group B beta-hemolytic streptococcal meningitis in a neonate. *J Pediatr* 1976;88:289-291.
5. Adams JM, Kenny JD, Rudolph AJ: Central diabetes insipidus following intraventricular hemorrhage. *J Pediatr* 1976;88:292-294.
6. Giacoia GP, Watson S, Karathanos A: Treatment of neonatal diabetes insipidus with desmopressin. *South Med J* 1984;77:75-77.
7. Fenton LJ, Kleinman LI: Transient diabetes insipidus in a newborn infant. *J Pediatr* 1974;85:79-81.
8. Greger NG, Kirkland RT, Clayton GW, et al: Central diabetes insipidus: Twenty-two years' experience. *AJDC* 1986;140:551-554.
9. Chanson P, Jedynak CP, Dabrowski G, et al: Ultralow doses of vasopressin in the management of diabetes insipidus. *Crit Care Med* 1987;15:44-46.
10. Levitt MA, Fleischer AS, Meislin HW, et al: Acute post-traumatic diabetes insipidus: Treatment with continuous intravenous vasopressin. *J Trauma* 1984;24:532-535.
11. Kaplowitz PB, D'Ercole AJ, Robertson GL: Radioimmunoassay of vasopressin in familial central diabetes insipidus. *J Pediatr* 1982;100:76-81.
12. Fluid and electrolyte therapy, in Rowe P (ed): *The Harriet Lane Handbook*, ed 11. Chicago, Year Book Medical Publishers Inc, 1987, pp 230-238.
13. Hays RM: Agents affecting the renal conservation of water, in Gilman AG, Goodman LS, Rall TW, et al (eds): *The Pharmacological Basis of Therapeutics*, ed 7. New York, MacMillan Publishing Co Inc, 1985, pp 915-917.
14. Gennari FG: Serum osmolality: Uses and limitations. *N Engl J Med* 1984;310:102-105.

In Other AMA Journals

JAMA

Periconceptional Use of Multivitamins and the Occurrence of Neural Tube Defects

J. Mulinare; J. F. Cordero; J. D. Erickson; R. J. Berry (*JAMA* 1988;260:3141)

The Changing Epidemiology of Reye's Syndrome in the United States: Further Evidence for a Public Health Success

E. S. Hurwitz (*JAMA* 1988;260:3179)

Infections and Sickle Cell Disease in Eastern Saudi Arabian Children

Mohamed I. El Mouzan, MD; Baker H. Al Awamy, MD; Gamil Absood, PhD

• The rate and pattern of infections in 144 Saudi Arabian children with sickle cell disease (SCD) and matched normal control subjects are reported. All diagnoses of SCD were made at birth by means of screening blood from the umbilical cord. The children were prospectively followed up from birth to 4 years of age. Severe bacterial infections occurred in none of the children with SCD; one of the control children developed pneumococcal meningitis. Acute gastroenteritis was significantly more common among patients with SCD. For the first year of life, patients with SCD had significantly more infections than did the control children; but the reverse was true in the group that was 37 to 48 months of age. Considering all types of infections for all age groups, no difference was noted between patients with SCD and control subjects in terms of infection rate or related hospital admission. There were no deaths caused by infection in this series. We conclude that Saudi Arabian infants and young children of oasis origin with SCD are not at increased risk of infections compared with healthy children of the same age.

(*AJDC* 1989;143:205-207)

In patients with sickle cell disease (SCD), infections are major causes of morbidity and mortality, particularly in early childhood. Bacterial infections such as pneumococcal septicemia, meningitis, and salmonella osteomyelitis are more prevalent and more severe in patients with SCD than in the normal population.[1-4] However, common viral infections are believed to be neither more common nor more severe in patients with SCD than in the normal population.[5] In early reports from the Eastern Province of Saudi Arabia, where SCD has attracted worldwide interest, investigators described a clinically milder form of SCD[6-8] than that described in reports from America and Jamaica; however, subsequent investigations showed the opposite to be true in a subset of Saudi Arabian patients of southwestern origin.[9,10]

We collected data prospectively from a cohort of children with SCD and from children serving as control subjects. Our objective was to define the pattern and rate of infections in a homogeneous subpopulation of children with SCD in the Eastern Province of Saudi Arabia.

PATIENTS AND METHODS

This study is part of the SCD research project established in 1982 at King Faisal University, Dammam, Saudi Arabia. The three major general hospitals in the area, Dammam Central Hospital, Qatif General Hospital, and King Fahd Hospital of the University, were coordinated to provide umbilical cord blood samples. After delivery, blood from the placental end of the umbilical cord was collected in 5-mL tubes containing edetic acid as the anticoagulant. The samples were received daily, except Friday, by the research laboratory at the university. All samples were examined by cellulose acetate electrophoresis in a TRIS–edetic acid–borate buffer at a pH of 8.4. All cases with an electrophoretic pattern indicating the presence of hemoglobins F and S (FS pattern), as well as those that were doubtful, were investigated by agar gel electrophoresis (pH, 6.4) to confirm the diagnosis. All newborns with an FS electrophoretic pattern were retested on their first clinic visit to exclude any possibility of misdiagnosis.

After the completion of hemoglobin electrophoresis, an Arabic-speaking nurse or social worker would visit the mothers of the neonates that were FS positive before they were discharged from the hospital. The nurse would explain the provisional diagnosis to each mother and stress the importance of follow-up. The mothers were then given an appointment for the initial clinic visit at the project clinic nearest their residence. Control subjects were selected from the newborns who were normal at birth and whose hemoglobin electrophoretic pattern was normal. They were matched according to maturity, sex, and closest date of birth. Follow-up examinations occurred every one to three months in the first year, every three to four months during the second year, and every six months thereafter. For the convenience of the parents, three clinics were established in the three participating hospitals, for the purpose of follow-up of patients and control subjects. These clinics were conducted on a regular basis by the project team (ie, pediatricians, nurse, and social worker). At each visit, history and physical examinations were performed, with particular emphasis on infections, outpatient visits, hospitalizations, and diagnoses made during the interval period. The diagnosis of infections was based on clinical grounds and on results of the necessary routine investigations, but no special microbiological studies were performed. Decisions concerning laboratory investigations, roentgenographic examinations, treatment, and hospitalization were made by the treating pediatrician. Attendance of the project clinic was encouraged by the provision of expert medical care during and outside of clinic hours, free transportation, and incentives to children. Attempts to minimize defaults were made by the establishment of a good relationship with the parents through a friendly attitude of the clinic staff, avoidance of embarrassing questions, minimization of blood sampling from infants, and home visits to the families by the social worker. Further details on the methodology, organization, and preliminary results of this project have been described elsewhere.[11,12]

Statistical analysis consisted of crude and modified Mantel-Haenszel χ^2 tests for comparison of the rate of infections, and Fisher's exact test for comparison of hospital admissions in patients with SCD and in control subjects.

RESULTS

From 1982 to 1987, 144 children with SCD and an equal number of control

Accepted for publication Oct 4, 1988.

From the Departments of Pediatrics (Drs El Mouzan and Al Awamy) and Community Medicine (Biostatistics) (Dr Absood), Colleges of Medicine and Medical Sciences, King Faisal University, Dammam, Saudi Arabia.

Reprint requests to King Fahd Hospital of the University, PO Box 40026, Al Khobar 31952, Saudi Arabia (Dr El Mouzan).

Table 1.—Rates of Clinical Infection in Patients With Sickle Cell Disease (SCD) and in Control Subjects

Type of Infection	Infection Rates*		Crude χ^2	*P* Value
	Patients With SCD	Control Subjects		
Upper respiratory tract	40	37.6	0.6766	.4
Bronchopneumonia	2.0	2.1	0.0076	.9
Tonsillitis	3.2	3.4	0.0126	.09
Acute gastroenteritis	14.8	10.7	4.1565	.04
Others†	3.8	5.0	0.7649	.3
All infections	63.8	58.8	2.7739	.09

*Calculated by dividing number of episodes by number of patient half-years times 100.
†Includes otitis media, croup, urinary tract infection, and one case of pneumococcal meningitis in a control subject.

Table 2.—Distribution of Rates of Clinical Infection According to Age Group*

Age, mo	Infection Rates		Crude χ^2	*P* Value
	Patients With SCD	Control Subjects		
≤12	79.9	66.8	11.4884	.0007
13-24	65.2	56.8	1.9608	.1
25-36	37.8	40.4	0.1353	.7
37-48	14.3	58.3	16.6172	.0001

*SCD indicates sickle cell disease.

Table 3.—Hospital Admissions for Infection*

Type of Infection	Patients With SCD		Control Subjects		FET *P* Value
	No.	Admissions	No.	Admissions	
Upper respiratory tract	222	2	201	0	.2
Bronchopneumonia	11	7	11	3	.06
Acute gastroenteritis	82	5	57	1	.2
Others	21	2	27	2	.8

*SCD indicates sickle cell disease; FET, Fisher's exact test.

subjects were examined and evaluated. They were all from the Eastern Province of Saudi Arabia. The distribution of SCD genotypes was 127 SS and 17 S β-thalassemia. We followed up 132 patients to the age of 12 months, and 79, 45, and 21 patients to the ages of 24, 36, and 48 months of age, respectively. This represents 1140 patient clinic visits and 544 patient half-years. The corresponding rates for healthy children serving as control subjects were as follows: 128 children were followed up to the age of 12 months, and 74, 47, and 18 were followed up to the ages of 24, 36, and 48 months, respectively, representing 1030 patient clinic visits and 534 patient half-years.

Throughout the four-year study period, no patient with SCD had a severe bacterial infection, but one of the control children had pneumococcal meningitis at 4 months of age and recovered uneventfully. The rates of common, less severe clinical infections documented in patients with SCD and in normal control subjects are shown in Tables 1 and 2. There were 14.8 and 10.7 episodes of acute gastroenteritis per 100 patient half-years for patients with SCD and for control subjects, respectively. Except for acute gastroenteritis ($P = .04$), there was no significant difference between children with SCD and control subjects (Table 1). In the up-to-12-months-of-age group, patients with SCD had a significantly higher rate of infection ($P = .0007$), while the reverse was true in the 37- to 48-months-of-age group ($P = .0001$). Nevertheless, when all infections in all age groups were considered, patients with SCD and control subjects had 63.8 and 58.8 episodes of infection per 100 patient half-years, respectively, a difference that is not significant ($P = .09$). In addition, when the modified Mantel-Haenszel χ^2 test was performed (stratification according to age), the results were consistent with those of the crude χ^2 test, indicating that age was not a contributing factor.

Hospital admissions for infections in patients with SCD and in control subjects are listed in Table 3. For each and all infections, there was no significant difference between children with SCD and control subjects in terms of hospital admissions ($P > .05$). No deaths from infection occurred in this series.

COMMENT

Sickle cell disease in the Eastern Province of Saudi Arabia has been reported to be more benign than in other populations.[7,8] However, physicians practicing in this area are becoming aware of the existence of two forms of SCD, severe and mild. The severe form occurs in patients whose ethnic background is from the southwest Arabian Peninsula, while the mild form occurs in patients of oasis origin in the Eastern Province (ie, Al-Hasa and Qatif). To our knowledge, prospective controlled studies on infections in either subpopulation have not been performed. Because of the importance of the mild form of SCD for future research, this article describes the pattern and rates of infection in a representative, unbiased sample of patients with SCD who are of oasis origin.

The documentation of pneumococcal meningitis in one of the control subjects and the lack of occurrence of this infection in patients with SCD indicate that, despite the presence of this pathogen in the community, children with SCD who are of oasis origin were not more susceptible to severe pneumococcal infection than were normal control subjects. These findings conflict with the very high risk of infection reported in American and Jamaican patients. Furthermore, our patients appeared to be even less prone to bacterial infection than patients described in previous reports from the same area.[7,8] It is possible that these other studies had included pa-

tients of other ethnic origin who reside in the Eastern Province. Immunologic disorders and splenic dysfunction increase the risk and severity of infection in patients with SCD.[13-15] An earlier study of the same subpopulation indicated that Saudi Arabian patients with SCD had normal or nearly normal spleen function compared with American patients with SCD, who had markedly decreased spleen function. The relative preservation of spleen function in patients of eastern origin appears to be an important protective factor against bacterial infection.[16]

In this study, upper and lower respiratory tract infections were neither more common nor more severe in patients with SCD than in control subjects, while acute gastroenteritis was significantly more common in patients with SCD. When all infections were analyzed according to age (Table 2), the difference was highly significant in the up-to-12-months-of-age group; but in the 37- to 48-months-of-age group, control subjects had more infections than did patients with SCD, a finding that is currently difficult to explain. When all infections for all age groups were considered, there was no significant difference in infection rates between patients with SCD and controls ($P = .09$). This finding supports the general impression that nonbacterial infections are neither more prevalent nor more severe in patients with SCD than in the normal population.

Hospital admissions for infections as a measure of morbidity and, perhaps, of severity were not significantly more common in patients with SCD, indicating that most of these infections were mild enough to be managed on an outpatient basis. The absence of fatality from infections was not surprising, in view of the benign nature of infections described in this report. Such observation is in sharp contrast with the high mortality resulting from infections in all other populations.[7,17,18] We conclude that, of the infants and young children with SCD living in the Eastern Province of Saudi Arabia, those of eastern origin do not have an increased risk of infection and that infections are not more severe than those in normal control subjects. Further research is needed to identify the factors that are protecting these children against severe infections.

This study was supported in part by grant AR-093 from King Abdulaziz City for Science and Technology, Riyadh, Saudi Arabia.

References

1. Barrett-Conner E: Bacterial infection and sickle cell anemia. *Medicine* 1971;50:96-112.
2. Overturf GD, Powers D, Baraff LJ: Bacterial meningitis and septicemia in sickle cell disease. *AJDC* 1977;131:784-787.
3. Pearson HA: Sickle cell anemia and severe infections due to encapsulated bacteria. *J Infect Dis* 1977;136:S25-S30.
4. Kabins SA, Lerner C: Fulminant pneumococcemia and sickle cell anemia. *JAMA* 1970;211: 467-471.
5. Rosse WF: Infections in sickle cell disease, in Walter Fried (ed): *Comparative Aspects of Sickle Cell Disease*. Amsterdam, Elsevier Science Publishers, 1982, pp 63-71.
6. Perrine RP, Brown MJ, Clegg GB, et al: Benign sickle cell anemia. *Lancet* 1972;2:1163-1167.
7. Perrine RP, Pembrey ME, John P, et al: Natural history of sickle cell anemia in Saudi Arabs: A study of 270 subjects. *Ann Intern Med* 1978;88:1-6.
8. Perrine RP, John P, Pembrey ME, et al: Sickle cell disease in Saudi Arabia in early childhood. *Arch Dis Child* 1981;56:187-192.
9. Babiker MA, Taha SA: Two different patterns of sickle cell disease in children in Saudi Arabia. *Ann Trop Paediatr* 1982;2:179-181.
10. Acquaye JK, Omer A, Ganeshaguru K, et al: Non-benign sickle cell disease in western Saudi Arabia. *Br J Haematol* 1985;60:99-108.
11. Al Awamy BH, El Mouzan MI, Al Torki M, et al: Neonatal screening for sickle cell disease in the Eastern Province of Saudi Arabia. *Trans R Soc Trop Med Hyg* 1984;78:792-794.
12. Al Awamy BH, El Mouzan MI, Al Torki M, et al: Newborn screening for sickle cell hemoglobinopathy and other erythrocyte inherited disorders in the Eastern Province of Saudi Arabia. *Saudi Med J* 1986;7:502-509.
13. Pearson HA, Spencer RP, Cornelius EA: Functional asplenia in sickle cell anemia. *N Engl J Med* 1969;281:923-925.
14. Johnstone RB, Newman SL, Struth AG: An abnormality of the alternate pathway of complement activation in sickle cell disease. *N Engl J Med* 1973;288:803-808.
15. Bjorson AB, Gaston MH, Zellner CL: Decreased opsonization for *Streptococcus pneumoniae* in sickle cell disease: Studies on selected complement components and immunoglobulins. *J Pediatr* 1977;91:371-378.
16. Al Awamy BH, Wilson WA, Pearson HA: Splenic function in sickle cell disease in the Eastern Province of Saudi Arabia. *J Pediatr* 1984;104: 714-717.
17. Powars DR: Natural history of sickle cell disease: The first ten years. *Semin Hematol* 1975;12:267-285.
18. Rogers DW, Clarke JM, Cupidore L, et al: Early death in Jamaican children with sickle cell disease. *Br Med J* 1978;1:1515-1516.

In Other AMA Journals

JAMA

Efficacy of Mandatory Seat-belt Use Legislation

T. L.Chorba; D. Reinfurt; B. S. Hulka (*JAMA* 1988;260:3593)

Prospective Study of the Effect of Safety Belts on Morbidity and Health Care Costs in Motor-Vehicle Accidents

E. M. Orsay; T. L. Turnbull; M. Dunne, J. A. Barrett; P. Langenberg; C. P. Orsay (*JAMA* 1988;260:3598)

The Efficacy and Safety of Home Nebulizer Therapy for Children With Asthma

Deborah A. Zimo, MD; Michele Gaspar, RN; Javeed Akhter, MD

• We evaluated the efficacy and safety of nebulized β-agonists used in the homes of 22 children with asthma. Patients served as their own controls for the comparison of asthma-related variables between periods of 12 months before and 12 months after the initiation of home nebulizer therapy. Significant reductions in the numbers of emergency department visits, hospital admissions, and short courses of prednisone therapy occurred when home nebulizer therapy was provided. The younger the patients, the more frequently improvement occurred. After the initiation of home nebulizer therapy there was no change in the severity of illness when patients presented to the emergency department or in the number of episodes of respiratory failure. Home nebulizer therapy for children with asthma appears safe and reduces the need for hospital care and short courses of prednisone therapy.

(*AJDC* 1989;143:208-211)

Air compressor–driven nebulizers are widely used for the administration of β-agonists to patients treated for acute asthma in emergency departments or inpatient units. They are also becoming accepted as part of the home therapy for asthma. Data concerning the efficacy and safety of this form of treatment, however, are scant. Available studies, which deal almost exclusively with adult patients with severe asthma, have found home nebulizer therapy effective in improving symptoms but not in reducing the need for emergency department treatment or hospitalization.[1-4] One retrospective study of children with asthma did find a significant decrease in hospital admissions and inpatient days following the initiation of home nebulizer therapy.[5] The safety of nebulizer therapy at home has been evaluated primarily by analyses of its use among patients dying of asthma. While there is no evidence for excess mortality among patients using nebulizers at home,[3,4,6] other forms of morbidity have not been examined.

This retrospective study evaluates the efficacy and safety of nebulized β-agonists used in the home for the management of acute episodes in children with perennial asthma. The numbers of emergency department visits, hospital admissions, days hospitalized, and frequency of administration of short courses of prednisone therapy were evaluated in relation to outcome. There is concern about the use of nebulizers at home based on the possibility that patients will rely excessively on their nebulizers and delay seeking medical attention for acute exacerbations of asthma. Accordingly, we assessed safety by evaluating the following: (1) the severity of illness at the time of presentation to the emergency department, (2) the number of episodes of respiratory failure, and (3) the frequency of side effects occurring during the administration of nebulized β-agonists in the emergency department.

PATIENTS AND METHODS

Patients

We reviewed the charts of all patients for whom a nebulizer for home use was prescribed between August 1982 and September 1983 at La Rabida Children's Hospital and Research Center, Chicago. La Rabida, the long-term–care facility of the University of Chicago Department of Pediatrics, provides continuous care for children with chronic illnesses, including asthma. The population of children with asthma served is largely composed of disadvantaged, inner-city minority groups. Data were collected for those patients whose primary diagnosis was asthma. To allow for seasonal variations in the manifestation of asthma symptomatology, only patients who had been followed up for at least 12 months before and 12 months after receiving their home nebulizers were included in the study. Patients served as their own controls for the comparison of asthma-related variables before and after the initiation of home nebulizer therapy. Because it was difficult to obtain uniform medical data from other facilities, only patients who received all their care at our institution were studied. Patients are routinely queried regarding visits to other facilities during clinic evaluations or on admission to La Rabida.

Methods

Data abstracted from the charts included the patient's age at the institution of home nebulizer therapy, sex, and race. For the 12 months before and after home nebulizer treatment was initiated, the following data were collected: (1) the frequency of use of short courses of oral prednisone therapy (usually 1 mg/kg twice daily for three to five days), (2) other medications prescribed for asthma, (3) the frequency and duration of hospitalizations, (4) the number of emergency department visits for asthma, and (5) the number of episodes of respiratory failure.

In our emergency department, arterial blood gas values are obtained routinely for any patient with clinical signs suggestive of respiratory failure, eg, persistence, after initial treatment with one dose of subcutaneous epinephrine and one dose of a nebulized β-agonist, of pulsus paradoxus, moderate to severe retractions, or a low peak expiratory flow rate. The presence of an arterial oxygen tension less than 50 mm Hg for patients breathing room air or an arterial-alveolar oxygen ratio less than 0.5 for patients receiving supplemental oxygen is considered type I respiratory failure. Type II respiratory failure is defined as an arterial carbon dioxide tension greater than 50 mm Hg, regardless of the arterial oxygen tension.

Records of emergency department visits were searched for the presence of complications resulting from therapy. These included the occurrence of tremors, headache, chest pain, or cardiac arrhythmias during or immediately following treatment with a nebulized β-agonist. The protocol for administration of these agents at La Rabida mandates recording these signs and symptoms.

The severity of asthma at each emergency department visit was scored according to the system outlined in Table 1. The presence of any of the scored variables is routinely recorded in the medical chart by the emergency department nurse whenever a patient is treated for asthma at La Rabida. Because

Accepted for publication Nov 14, 1988.

From La Rabida Children's Hospital and Research Center, Chicago, and the Department of Pediatrics, Pritzker School of Medicine, University of Chicago.

Reprint requests to La Rabida Children's Hospital, East 65th Street at Lake Michigan, Chicago, IL 60649 (Dr Zimo).

Table 1.—Variables Used for Scoring Asthma Severity in the Emergency Department

Variable	Score: If Present	Score: If Absent
Moderate to severe anxiety	1	0
Diaphoresis	1	0
Severe retractions	1	0
Pulsus paradoxus ≥10 mm Hg	1	0
Peak expiratory flow rate <20% of patient's previous best	1	0
Oxygen administration*	1	0
Arterial blood gas determination performed*	1	0
Visible central cyanosis	2	0
Other central nervous system signs	2	0
Type I respiratory failure	2	0
Type II respiratory failure	3	0
Maximum	12	. . .
Minimum	. . .	0

*Not scored if the patient also had respiratory failure by the arterial blood gas criteria.

supplemental oxygen and arterial blood gas analysis are not usually provided for patients treated for uncomplicated asthma in our emergency department, their inclusion in emergency department care was thought to reflect a greater level of concern on the part of the examining physician and, thus, to indicate greater severity of the acute episode, even when the patient was not experiencing type I or type II respiratory failure. Although this is speculative, we wished to err on the side of excessive caution to avoid overlooking severe episodes. However, to avoid overweighting these two measurements, they were not scored if the patient was also experiencing respiratory failure.

The average emergency department severity score was determined for each patient for the 12 months before and 12 months after the institution of home nebulizer therapy by dividing the sum of the severity scores by the number of emergency department visits.

Statistical Analysis

The simple paired Student *t* test was used to compare frequencies before and after the initiation of home nebulizer therapy. Data were analyzed for differences in the number of emergency department visits, frequency of hospital admissions, number of hospital days, frequency of short courses of oral prednisone therapy, number of episodes of respiratory failure, and average emergency department severity scores.

The relationship between treatment outcome and patient age was further analyzed using linear and multiple regression analyses after controlling for confounding variables.

Table 2.—Comparison of Variables Before and After Institution of Home Nebulizer Therapy*

Variable	Before Institution of Nebulizer Therapy	After Institution of Nebulizer Therapy	P
No. of emergency department visits	6.32 (3.80)	3.50 (3.00)	.003†
No. of hospital admissions	3.36 (2.30)	2.23 (2.33)	.05†
No. of days hospitalized	18.96 (19.22)	15.00 (27.73)	.47
No. of prednisone bursts	3.41 (2.52)	2.18 (2.38)	.04†
No. of episodes of respiratory failure	0.27 (0.55)	0.36 (0.79)	.61
Average emergency department severity score	0.96 (0.81)	0.70 (1.06)	.18

*Values are mean (SD).
†Statistically significant.

RESULTS

Between August 1982 and September 1983, nebulizers were prescribed for home use for 84 patients. Twenty-two of these patients met the study criteria. Of the 62 who did not, 26 (42%) had been followed up at La Rabida for less than 12 months before receiving a home nebulizer, and one (2%) had a primary diagnosis of bronchopulmonary dysplasia. Follow-up data were incomplete for the remaining 35 patients (56%), who received only part of their care at our institution or transferred their care elsewhere within 12 months of receiving a nebulizer for home use.

Of the 22 patients for whom complete data were available, 14 (64%) were male, eight (36%) were female, 21 (95%) were black, and one (5%) was Hispanic. The ages of the patients at the time they received the home nebulizers ranged from 3 to 17 years, with a mean of 8 years. All patients were given oral theophylline daily throughout the study period and received doses of oral β-agonists as daily maintenance or as needed. Eleven patients received oral or inhaled steroids as maintenance for varying periods during the study. When the 12 months before were compared with the 12 months after the initiation of home nebulizer therapy, maintenance steroid requirements increased in four patients, decreased in four, and remained constant in three. The medications prescribed for use in the home nebulizer were metaproterenol sulfate for 17 patients, metaproterenol plus cromolyn sodium for three patients, and terbutaline sulfate (an aqueous solution marketed for parenteral use) for two patients. Six patients used their nebulizers at fixed intervals three or four times daily; 16 used them only when needed for acute exacerbations. All patients had been instructed to use a fixed dose of β-agonist for the nebulizer treatments and to contact their physician or go to the emergency department if they required more than a given number of treatments (usually four to six) within a 24-hour period or if they needed treatments at intervals of less than three hours.

A statistically significant reduction in the number of emergency department visits and hospital admissions and in the frequency of use of short courses of prednisone therapy was found between periods when the patients used nebulized β-agonists at home compared with periods when they did not (Table 2). There was no difference in the number of days of hospitalization despite a significant decrease in the number of admissions, suggesting a longer duration of individual hospital stays. This was the case for eight patients. For three of these patients the increase in duration of hospitalizations was marked; one patient had no admissions before and a single ten-day hospitalization after home nebulizer therapy was begun, and the other two patients had increases

from two and 7.7 days per hospitalization to 3.7 and 16.1 days per hospitalization, respectively. However, nine patients had shorter hospital stays after initiating home nebulizer therapy, and another five patients who had been hospitalized in the year before receiving a home nebulizer had no admissions in the year following.

There was no difference between the periods before and after the initiation of home nebulizer therapy in the average severity of illness at the time patients presented to the emergency department. Similarly, there was no statistically significant difference in the number of episodes of respiratory failure between the two periods. In the 12 months before nebulizer therapy was available at home, five episodes of type I respiratory failure occurred among four patients, and an additional patient had one episode of type II respiratory failure. In the 12 months after home nebulizer therapy was available, six episodes of type I respiratory failure occurred in four patients, and two patients each had one episode of type II respiratory failure. Altogether, eight patients experienced episodes of respiratory failure, three patients had respiratory failure only during the period before home nebulizer therapy was available, three had respiratory failure only afterward, and two had respiratory failure during both periods. No patient experienced cardiac arrhythmias or other serious complications attributable to the use of nebulized β-agonists.

There is a known tendency of asthma to improve spontaneously in school-age children. We examined the effect of age to determine whether it alone could account for the improvements seen with home nebulizer therapy in our patients. At the univariate level, age was inversely correlated to the number of emergency department visits ($r = -.364$), number of hospital admissions ($r = -.378$), frequency of use of short courses of prednisone therapy ($r = -.103$), and number of episodes of respiratory failure ($r = -.183$) in the period before the institution of home nebulizer therapy. That is, the younger the patient, the greater the number of emergency department visits, admissions, and episodes of respiratory failure and the more frequent the use of short courses of prednisone therapy, though this is barely statistically significant. No such relationship was found between age and these variables after home nebulizer therapy was instituted. The correlation coefficients for the relationship with age were positive for emergency department visits ($r = .222$), hospital admissions ($r = .056$), and short courses of prednisone therapy ($r = .229$) but remained negative for episodes of respiratory failure ($r = -.129$) in the period following the institution of home nebulizer therapy. Thus, there was a tendency for the older patients to have greater numbers of emergency department visits and hospital admissions in the period after the institution of home nebulizer therapy. This could mean that younger children improved more with nebulizer therapy or that the older children had more severe disease.

Two variables, the numbers of emergency department visits and hospital admissions, were reclassified to reflect the change in frequency after the institution of home nebulizer therapy using the frequency before such therapy was initiated as a baseline level for comparison. When the frequency was increased compared with the baseline a score of 1 was assigned, when it was decreased the score was 3, and when it was the same a score of 2 was given. A composite score was derived for these two variables as a measure of the degree of improvement. Using this definition, improvement was inversely related to age at the univariate level ($r = -.438$); that is, the younger the child, the more likely there was to be a decrease in emergency department visits and hospital admissions following the institution of home nebulizer therapy.

Multiple regression analysis was performed using the improvement score as the dependent variable and including in the model age, number of episodes of respiratory failure in the period before home nebulizer therapy, use of prednisone therapy before and after home nebulizer therapy was started, and severity scores after the institution of home nebulizer therapy. Age ($\beta = -.153$, $P = .04$) and the number of short courses of prednisone therapy after the institution of home nebulizer therapy ($\beta = -.334$, $P = .004$) were independently inversely related to the reduction in emergency department visits and hospital admissions. That is, younger children and also those who received fewer short courses of prednisone therapy after starting home nebulizer therapy had greater reductions in emergency department visits and admissions. Age alone explained 19.2% and the number of short courses of prednisone therapy after the institution of home nebulizer therapy alone explained 34% of the observed variance in the reduction in emergency department visits and hospital admissions. When age and the number of short courses of prednisone therapy were both included in the model using multiple regression analysis, age did not have a significant relation to the reduction in these measurements ($\beta = -.112$, $P = .085$). This was because the use of short courses of prednisone therapy nafter the institution of home nebulizer therapy increased with increasing age ($r = .229$).

COMMENT

Our data suggest that home nebulizer therapy for children with perennial asthma in a disadvantaged, inner-city environment reduces the need for emergency department care, hospitalization, and oral steroid therapy, at least among younger children, but it does not reduce the overall severity of illness as judged by the need for maintenance steroid therapy or the occurrence of respiratory failure. Previous studies of adults with asthma found an association between home nebulizer therapy and improvement in symptoms, peak expiratory flow rates, and the need for oral steroids[1,2] but found no reduction in the number of days of hospitalization, hospital admissions, sick leave days, or outpatient consultations.[2,3] However, these studies examined either patients with severe, chronic asthma, which was poorly controlled with conventional home therapy, or a mixed group of patients with asthma and bronchitis. Our patients were children with perennial, reversible asthma who were not purposefully selected for poor disease control.

Two studies have evaluated home nebulizer therapy for children with asthma by using mailed questionnaires to elicit parental perceptions of the efficacy of this treatment.[4,5] Although parents reported a broad range of disease severity and dosage and frequency of use of nebulized β-agonists and other prophylactic treatment for asthma,

most reported an improvement in symptoms and a reduction in hospital admissions following the institution of home nebulizer therapy. In one of these studies,[5] review of the medical records of 27 children confirmed the parents' reports of a significant decrease in hospital admissions and inpatient days when identical time periods before and after the commencement of home nebulizer therapy were compared. Changes in steroid requirements and the severity of acute episodes were not evaluated.

Concerns with using nebulized β-agonists in the home include the possibility of decreased responsiveness over time to these agents and the potential for overreliance on nebulizer therapy, resulting in delay in seeking medical attention. Safety is of particular concern in children, since surveys of parental practice suggest that the manner in which parents actually administer nebulized medications in the home may deviate substantially from the usual recommendations with regard to dosage, frequency, and consultation with a physician.[4,5] No evidence of a decline in responsiveness to inhaled terbutaline has been found in adults four weeks after the initiation of twice-daily nebulizer treatments at home with this agent.[1] Reviews of deaths in adult asthmatic patients receiving nebulized β-agonists at home in Sweden and New Zealand found no excess mortality among these patients,[3,6] although delays in seeking medical attention because of reliance on home nebulizer therapy were thought to be possible or probable in small numbers of patients. Analysis of 75 deaths from asthma of patients receiving home nebulizer therapy in New Zealand revealed that death in these patients was associated with deficiencies in medical care similar to those seen in patients without nebulizers and that the probability that nebulized β-agonists contributed to death was lower than the probability that death would have occurred without them.[6]

We indirectly assessed the possibility that patients with home nebulizers delayed seeking medical care by scoring asthma severity in the emergency department, and we extended evaluation of the safety of this form of therapy to include analysis of the frequency of respiratory failure and serious complications due to nebulized β-agonists. The fact that there was no difference in the average severity of illness at the time patients presented to the emergency department after the institution of home nebulizer therapy compared with before such therapy was instituted argues that there was no significant delay in seeking help. Similarly, there was no difference in the number of patients who presented with respiratory failure before compared with after nebulizer therapy was initiated at home. Furthermore, no significant complications due to nebulized β-agonists occurred.

Caution is necessary in interpreting our data for several reasons. The number of patients is relatively small. This is largely a reflection of the fact that in recent years the trend at our institution has been toward early initiation of home nebulizer therapy for children who have severe asthma or a frequent need for hospital care. Few such patients have been followed up for 12 months before home nebulizer therapy was prescribed.

The use of the patients as their own controls introduces potential bias due to the unidirectional order in which treatment was assigned, ie, a period without nebulizer use always followed by a period with nebulizer use. We chose this approach due to the difficulty of identifying patients of similar age, disease severity, and psychosocial background followed up exclusively at our institution who did not have home nebulizers. While improvement in symptomatology from year to year occurs in children with asthma for a variety of reasons, it is unlikely that the significant reduction in the need for emergency department visits, hospitalizations, and short courses of oral steroid thrapy seen in our patients in the year after the institution of home nebulizer therapy was due to time alone. The trend for younger rather than older patients to improve with home nebulizer therapy suggests that improvement did not simply reflect the natural history of asthma. The frequency of use of short courses of prednisone therapy increased with increasing age in the period after the initiation of home nebulizer therapy. Our conclusion is further strengthened by the fact that age explained 19% and the requirement for short courses of prednisone therapy explained 34% of the observed variance in the reduction in emergency department visits and hospital admissions after the institution of home nebulizer therapy.

This is a retrospective study. Criteria for the prescription of home nebulizer therapy probably varied throughout the study population. While the data collected from chart review consisted only of items routinely recorded according to our institutional protocols, we cannot be entirely sure that all staff were equally conscientious in record keeping. Other potentially confounding variables, such as the influence of parental education regarding asthma management and the placebo effect of simply having a nebulizer at home, cannot be accurately assessed.

Our data suggest that home nebulizer therapy for children with perennial asthma who are receiving theophylline and oral sympathomimetics as maintenance treatment can be safe and effective in reducing the need for emergency department visits, hospitalization, and oral steroid therapy. The overall severity of illness as judged by the need for maintenance steroid therapy and the occurrence of respiratory failure was not affected. The cost of home nebulizer therapy is more than offset by the reduced need for hospital care. Patients provided with this form of therapy continue to need close medical supervision as well as detailed instruction in the appropriate use of nebulizers and in the need for prompt medical attention if nebulized β-agonists fail to provide appreciable, lasting relief for acute exacerbations of asthma.

We thank Edem Ekwo, MD, for assistance with statistical analysis and manuscript preparation.

References

1. McGivern DV, Ward M, Revill S, et al: Home nebulizers in severe chronic asthma. *Br J Dis Chest* 1984;78:376-382.

2. Boe J: Domiciliary nebulized beta-agonists: Long term treatment in asthmatics, and drug intake and plasma levels in acute asthma. *Eur J Respir Dis* 1984;136(suppl):193-203.

3. Andersson L, Boethius G: Effect of domiciliary treatment with nebulized beta 2-stimulants: A retrospective follow-up of 102 patients. *Eur J Respir Dis* 1984;136(suppl):205-212.

4. LaRoche CM, Harries AVK, Newton RCF, et al: Domiciliary nebulisers in asthma: A district survey. *Br Med J* 1985;290:1611-1613.

5. Ryan CA, Willan AR, Wherrett BA: Home nebulizers in childhood asthma: Parental perceptions and practices. *Clin Pediatr* 1988;27:420-424.

6. Sears MR, Rea HH, Fenwick J, et al: 75 Deaths in asthmatics prescribed home nebulisers. *Br Med J* 1987;294:477-480.

Exercise-Induced Differences in Cardiac Output, Blood Pressure, and Systemic Vascular Resistance in a Healthy Biracial Population of 10-Year-Old Boys

Frederick W. Arensman, MD; Frank A. Treiber, PhD; Michael P. Gruber; William B. Strong, MD

• Previous studies have documented systolic blood pressure differences in response to dynamic exercise when blacks were compared with whites. This study was performed to validate these data and to determine if the cardiac output and systemic vascular resistance responses to exercise are different in a biracial population of 10-year-old boys. Nineteen blacks and 31 whites underwent maximum supine graded exercise tests with Doppler determination of cardiac output and measurement of systolic and diastolic blood pressure and systemic vascular resistance. The blacks had a body surface area that was marginally larger than that of the whites, but no differences were noted in height or weight. Working capacities, when indexed by weight, were virtually identical between the two groups. No differences were noted in either systolic or diastolic blood pressure during preexercise, maximum exercise, or early and late recovery. White males had significantly higher cardiac indexes during preexercise, maximum exercise, and early and late recovery. Black males had greater systemic vascular resistance during preexercise, maximum exercise, and early and late recovery. Thus, the black children's blood pressure responses to exercise were comparable with those of the white children but they had a greater systemic vascular resistance and lower cardiac index. These racial differences may serve as potential markers for the prehypertensive state.

(*AJDC* 1989;143:212-216)

Accepted for publication Sept 12, 1988.

From the Pediatric Physical Performance Laboratory, Section of Pediatric Cardiology, and The Georgia Institute for Prevention of Human Disease and Accidents, Department of Pediatrics, Medical College of Georgia, Augusta.

Presented in part at the Southeastern Pediatric Cardiology Society Meetings, Charleston, SC, Sept 18, 1987.

Reprint requests to the Section of Pediatric Cardiology, Medical College of Georgia, Augusta, GA 30912-3710 (Dr Strong).

Despite recent reductions in cardiovascular mortality rates, essential hypertension continues to be a major cause of both morbidity and mortality in the United States.[1] The morbidity and mortality of essential hypertension in the United States is significantly greater in blacks than whites.[2] Investigators have begun to identify differences in cardiovascular reactivity that may account for some of these racial differences in essential hypertension.[3-5] Blacks have been found to exhibit greater cardiovascular reactivity to physical[6,7] and psychological stressors than have whites.[4] It has been postulated that greater systemic vascular resistance (SVR) is responsible for these blood pressure (BP) increases in blacks.[3,8,9] Our previous findings with normotensive children have documented greater BP response to upright exercise in black children than in whites.[6,7] Because mean arterial BP (MAP) is a product of SVR and cardiac index (CI),[10] increases in BP should be accompanied by increases in SVR and/or CI.

The purpose of this study was to evaluate the cardiovascular response to exercise of a healthy biracial population of 10-year-old boys, to measure BP and CI, and to calculate SVR changes in these normotensive boys during preexercise, maximum exercise, and recovery. Based on the above findings, we predicted that black boys would show greater BP increase and that this would be associated with greater SVR.

SUBJECTS AND METHODS

Fifty healthy 10-year-old boys (19 blacks and 31 whites) were recruited from local church and civic groups. A complete cardiovascular history was obtained from either the parent or guardian of each child. Each child received a complete cardiovascular examination by a pediatric cardiologist to help exclude cardiac disease. After the nature of the experiment had been explained, a parent or guardian granted informed consent and the child granted assent as approved by our institutional Human Assurance Committee. The children's hematocrit, height, and weight were measured and body surface area (BSA) was calculated using the West Nomogram.[11] Criteria for exclusion included a BSA below the third or above the 97th percentile for age,[12] resting BP above the 90th percentile for age,[13] or concurrent illness including sickle cell disease and/or anemia (hematocrit, <0.32). Based on these criteria, five children were excluded from participation. None of the participating children was a trained athlete.

The children reclined on an exercise table where an automated BP monitor (Critikon Dinamap model 1165) and electrocardiographic (ECG) leads for exercise ECG and timing of echocardiographic and Doppler events (Hewlett Packard model 77020AC) were attached. Five minutes after reclining on the exercise table, preexercise measurements of pulse, BP, aortic valve systolic area, and velocity of ascending aortic blood flow were made. Calculations of other indexes were performed after acquisition of the exercise test measurements.[14-16] Graded supine exercise testing was performed with an electronically braked cycle ergometer (Collins). Based on protocols previously established in our laboratory, work loads were determined by weight and were of three minutes' duration, and the child was urged to pedal to exhaustion.[6,7]

Blood pressures were measured in the right arm with the BP monitor instrument at rest and during the last 30 s of each exercise stage. The Critikon monitor has been validated for use during dynamic exercise testing.[17] Postexercise values were obtained from one to three minutes (early) and from three to five minutes (late) following cessation of exercise. Systolic, diastolic, and mean BPs were recorded at each phase. Appropri-

ate cuff size was used and the upper arm was relatively immobile because of the subject's position.

Heart rate was recorded at each stage of exercise from the ECG using the R-R interval. Prior to exercise, routine M-mode and two-dimensional echocardiograms were performed using the Hewlett-Packard model 77020AC system. Left ventricular size and septal and free wall thickness were measured and the ascending aorta at the aortic valve was visualized. Two-dimensional guidance was used to direct an M-mode beam for systolic measurement of aortic leaflet separation at the sinuses of Valsalva.[18] A second aortic valve interrogation was performed immediately following cessation of exercise to evaluate the possibility of an increased aortic size and increased separation of aortic valve leaflets during exercise. The method of calculating the flow area is shown in Fig 1: area of flow = $[(1/2)\text{diameter}]^2 \times 3.14$.

Doppler examination was performed using a 1.9-mH continuous-wave transducer placed in the suprasternal notch and directed toward the aortic valve. The beam was directed to achieve maximum flow velocity. It was assumed that this direction was parallel to aortic flow. The position was noted to facilitate subsequent interrogations.[18] Some other investigations have assessed velocity of flow in the ascending aorta rather than at the mitral valve. Because the aortic closure was frequently visualized on continuous-wave Doppler study and because of the ease of demonstrating aortic valve opening, we chose that site. Measurements of maximum velocity were made at preexercise, in the last 30 s of each exercise stage, immediately on completion of exercise, and between three and five minutes following exercise.

Computer analysis was employed to measure the peak velocity, the area under the velocity curve (the flow velocity integral), and the mean velocity at each of the described times. Peak velocity was plotted from the two greatest flow velocity peaks at each measured interval. The corresponding ejection times for the peaks were also plotted and the average was obtained. Figure 2 displays the plotting process. Shown also is the plotting method used to obtain time to ejection, time to peak ejection, and the flow velocity integral. The flow velocity integral, the area under the ascending aortic blood velocity curve, is the product of one half the peak velocity multiplied by ejection time.[14,19] Changes in the flow velocity integral have been shown to be proportional to changes in left ventricular stroke volume.[19] Cardiac output was calculated by the following formula: $CO = (V/2)(ET \times HR) \times AA$, in which CO indicates cardiac output in milliliters per minute; ET, ejection time in seconds; V, velocity in centimeters per second (V/2 equals

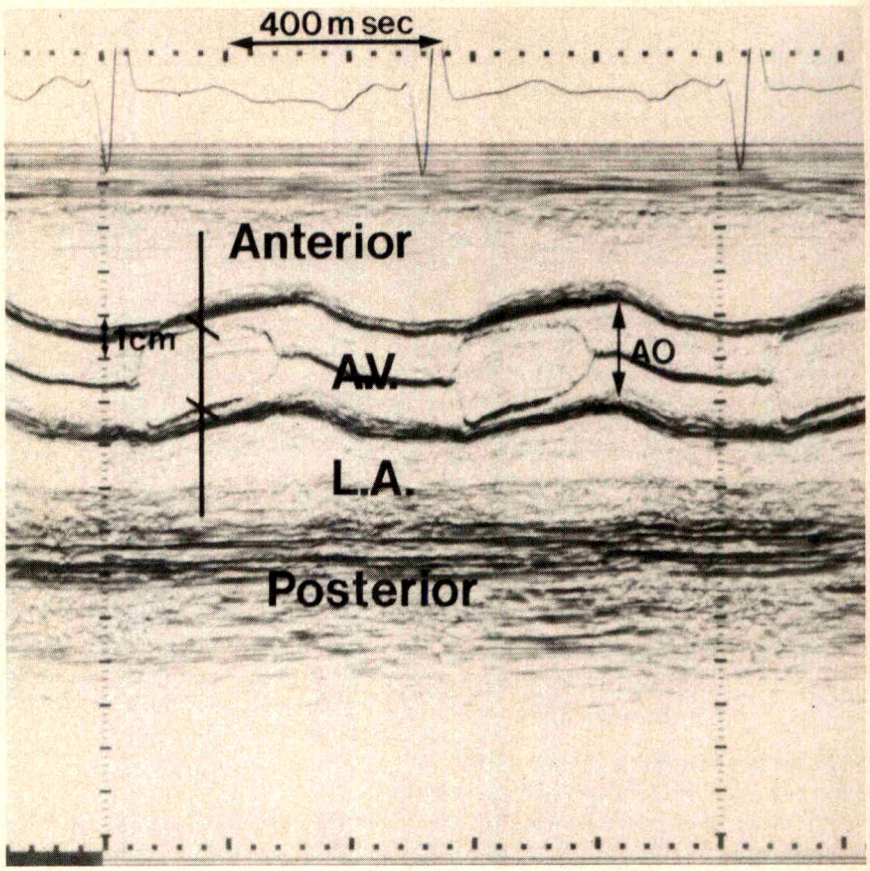


Fig 1.—Calculation of aortic flow area. M-mode echo derived from two-dimensional echo showing aorta (AO), aortic valve (AV), left atrium (LA), and measurement of AV opening diameter (crosshatches).

Fig 2.—Calculation of aortic velocity. Copy of typical Doppler trace from ascending aorta showing time from initial QRS deflection to ejection onset (TTE), ejection time (ET), flow velocity integral (FVI), and peak velocity of ejection (Pk). Time lines are every 200 ms and crosshatch denotes velocity of 1 m/s.

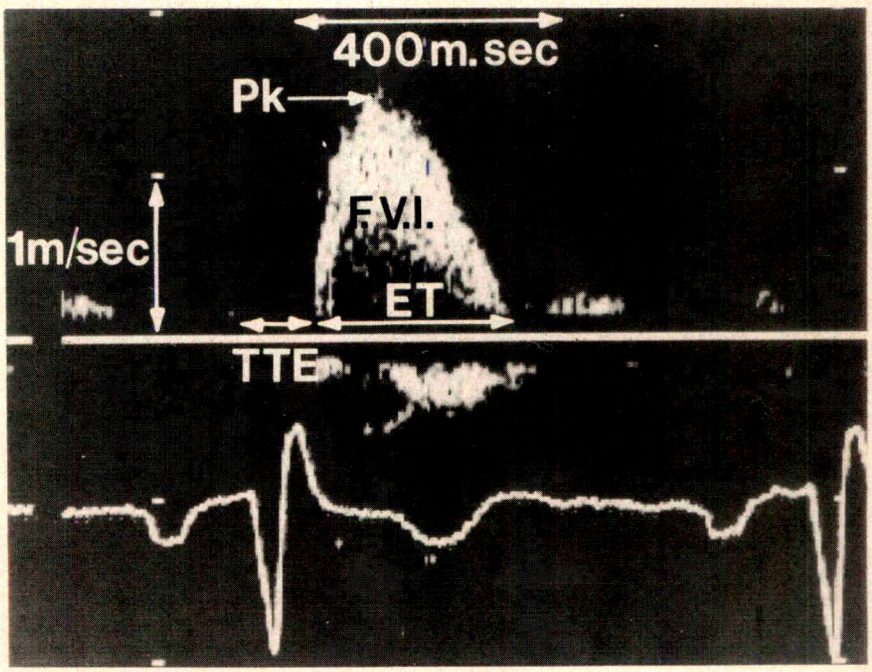


Table 1.—Anthropometric Variables by Race*

Anthropometric Variable	White	Black
Height, cm	140.27 ± 5.72	143.31 ± 6.16
Weight, kg	34.47 ± 5.88	36.69 ± 5.84
Body surface area, m^2	1.16 ± 0.11	1.22 ± 0.10
Quetelet index, kg/m^2	17.44 ± 2.20	17.79 ± 2.04

*All values are mean ± SD. No differences between races were significant ($P>.05$).

average velocity); HR, heart rate in beats per minute; and AA, aortic area in square centimeters.

The product of ejection time and heart rate gives the total time of ejection per minute. Cardiac output was divided by BSA to yield CI such that CI = CO/BSA in liters per minute per square meter. Systemic vascular resistance was recorded in Wood units, ie, SVR = MAP/CI in millimeters of mercury per liter per minute per square meter.

RESULTS

Anthropometrics

As presented in Table 1, although the black males tended to be larger than the white males, there were no significant differences in height ($P>.09$) or weight ($P>.28$) However, a trend was observed for BSA[11] ($P<.06$). There were no differences in body mass (ie, Quetelet index) by race. Blood pressure was analyzed using BSA as a covariate.

Physical Working Capacity

The slight difference in BSA between the groups resulted in the black boys starting their exercise at a higher mean work load than the white boys (186.1 ± 26.0 vs 163.5 ± 21.5; $P<.003$). Because the exercise test work loads increased every three minutes, there were significant differences at each stage. Because they began at lower work loads, the white boys exhibited a trend toward exercising longer ($P<.06$); however, the resultant maximum work load was not significantly different between the two groups (whites, 553.4 ± 72.8 kg/min; blacks, 582.7 ± 66.3 kg/min; $P>.17$). When physical working capacity was indexed by weight, the values for the two groups were virtually identical, with the whites averaging 16.3 kg/min/kg and the blacks averaging 16.2 kg/min/kg. These values are consistent with 50th-percentile values for previous studies performed in the sitting position on a cycle ergometer in our laboratory.[6]

Heart Rate

There were no significant differences in preexercise heart rates (in beats per minute) (blacks, 76.2 ± 11.73; whites, 80.7 ± 14.98; $P>.28$). Blacks had significantly lower heart rates at maximum exercise (blacks, 166.7 ± 17.17; whites, 177.5 ± 16.97; $P<.05$) and initial recovery (blacks, 107.0 ± 13.4; whites, 119.2 ± 19.6; $P<.05$).

BP

As shown in Table 2, when BSA was used as a covariable, systolic BP (in millimeters of mercury) was no different at preexercise (blacks, 106.7 ± 11.6; whites, 101.0 ± 10.1; $P>.05$), maximum exercise (blacks, 158.5 ± 19.7; whites, 147.5 ± 23.5; $P>.10$), and early and late recovery (blacks, 147.3 ± 19.6; whites, 138.8 ± 20.5 [early]; $P>.29$; and blacks, 107.6 ± 12.4; whites, 111.0 ± 12.1 [late]; $P>.10$).

When BSA was used as a covariable, diastolic BP was not significantly different during preexercise, maximum exercise, or recovery stages ($P>.13$, .24, .53, and .32, respectively).

Similarly, no differences were noted in mean BP during preexercise, maximum exercise, or early or late recovery stages ($P>.06$, .16, .33, and .84, respectively) when BSA was used as a covariable.

Aortic Leaflet Separation

No differences between groups or within groups were noted in aortic leaflet separation diameter at preexercise or following exercise (all P values $>.10$).

Ejection Time

No significant differences of ejection time were noted between the two groups at any assessment point (all P values $>.26$).

Change in Velocity Over Time

The change in velocity divided by the change in time was significantly lower in the blacks only at maximum exercise ($P<.006$). No significant differences were noted on all other comparisons (all P values $>.15$).

Time to Peak Ejection

Significant differences in time to peak ejection were present between the groups at maximum exercise, with whites having shorter time to peak ejection than blacks ($P<.02$).

CI

At each assessment point, whites had significantly higher CIs than blacks ($P<.003$, .001, .002, and .007, respectively).

SVR

Black children showed greater SVR during preexercise, maximum exercise, and early and late recovery ($P<.005$, .003, .0003, and .05, respectively).

Flow Velocity Integral

The flow velocity integral covaried by BSA was no different between the black males and white males at any of the exercise or recovery stages (all P values $>.19$).

Rate-Pressure Product

The rate-pressure product (systolic BP multiplied by heart rate) was virtually identical between the two groups at preexercise and maximum exercise and was not significantly different in either recovery stage (all P values $>.43$).

COMMENT

Previous studies have documented greater increases in systolic and/or diastolic BP in black children and adolescents than in white children exposed to physical exercise,[6,7] psychological stress,[4] and cold pressor stress.[5] The methods of this current study vary from previous works at our institution in that supine rather than upright exercise was performed. The supine position provides a better acoustic window for ultrasound evaluation as the ascending aorta remains posterior and the patient is rel-

Table 2.—Hemodynamic Variables for Each Exercise Stage by Race*

Hemodynamic Variable	Exercise Stage							
	Preexercise		Maximum		Initial Recovery		Final Recovery	
	White	Black	White	Black	White	Black	White	Black
Working capacity, kg/m/kg	NA	NA	16.30 ±72.75	16.20 ±66.26	NA	NA	NA	NA
Heart rate, BPM	80.69 ±14.98	76.22 ±11.73	177.50 ±16.97†	166.72 ±17.17	119.16 ±19.64†	107.88 13.40	103.04 ±16.20	101.41 ±16.20
Systolic blood pressure, mm Hg	101.00 ±10.11	106.72 ±11.62	147.49 ±23.48	158.51 ±19.66	138.76 ±20.48	147.29 ±19.58	111.04 ±12.07	107.59 ±12.35
Diastolic blood pressure, mm Hg	62.46 ±9.58	68.48 ±9.74	76.35 ±16.94	83.46 ±10.98	64.12 ±16.94	69.65 ±12.40	63.40 ±6.92	65.24 ±7.58
MAP, mm Hg	75.31 ±7.47	81.23 ±8.68	100.06 ±15.87	108.49 ±11.74	89.00 ±14.57	95.53 ±13.55	79.28 ±6.27	79.35 ±6.92
Ejection time, ms	287.42 ±31.91	281.11 ±41.89	189.35 ±20.44	196.56 ±21.87	237.96 ±26.96	246.35 ±35.62	259.40 ±34.02	259.59 ±37.64
dV/dT	1.84 ±0.77	1.87 ±0.47	3.26 ±1.02‡	2.45 ±0.68	2.93 ±1.28	2.43 ±0.79	2.53 ±1.24	2.17 ±0.36
Time to peak ejection, ms	71.69 ±19.64	64.28 ±9.07	52.23 ±14.61§	61.78 ±10.33	58.88 ±17.80	59.53 ±10.89	61.92 ±15.00	61.71 ±12.28
CI, CO/BSA (L/min/m²)	2.89 ±0.75†	2.24 ±0.55	5.77 ±1.31	4.47 ±1.11	4.75 ±1.17†	3.38 ±0.83	4.07 ±1.02†	3.24 ±0.81
SVR, MAP/CI (mm Hg/L/min/m²)	24.10 ±7.05†	31.20 ±8.67	15.28 ±3.20†	20.05 ±6.68	17.20 ±4.82‡	24.43 ±6.63	18.03 ±5.28§	22.04 ±7.59
Flow velocity integral	17.21 ±3.59	16.48 ±3.36	15.01 ±2.85	14.35 ±2.54	18.37 ±3.82	16.83 ±3.51	18.19 ±3.46	17.06 ±3.81
Rate-pressure product	8195 ±2004	8177 ±1432	26 233 ±5205	26 357 ±3815	16 534 ±3242	15 756 ±2765	11 534 ±2595	10 975 ±2423

*All values are mean ± SD. Differences between white and black subjects are not significant ($P>.05$) except where otherwise indicated. BPM indicates beats per minute; dV/dT, change in velocity over time; CI, cardiac index; CO, cardiac output; BSA, body surface area; SVR, systemic vascular resistance; MAP, mean arterial pressure; and NA, not applicable.

†$P<.01$ for difference between white and black subjects.

‡$P<.001$ for difference between white and black subjects.

§$P<.05$ for difference between white and black subjects.

atively immobile. Doppler study data acquisition is therefore facilitated. Other authors have demonstrated success with a similar technique in older children.[15] Recognizing that there are intrinsic differences in supine and upright exercise, a previous study in adults demonstrated that CI, peak flow velocity, and acceleration of flow are similar during both supine and upright exercise.[16] The current findings indicate that this technique is practical with relatively young children and the values obtained from this study are comparable to other reports of maximum responses for heart rate,[7,20] CI,[16,20] physical working capacity index,[6] and flow velocity integral.[14] In addition, it is noted that the aortic leaflet separation did not significantly increase during exercise and, thus, may not require further measurement if trends are being assessed. The use of the aortic valve rather than the ascending aorta as the area of flow may result in a lower cardiac output in the current study. However, the trends in cardiac output should be unaffected by the measurement site.

Previous work in our laboratory using upright cycle ergometry and measuring only SBP demonstrated that blacks tended to have greater BP response in the upright position when compared by BSA. The lack of such differences in the current study may be the result of hemodynamic differences in children's responses to upright vs supine exercise. However, this remains a question for future research. In previous studies, no racial differences were noted in preexercise BP.[6,7] Similarly, in the current study, racial differences were not present in preexercise systolic BP, diastolic BP, or MAP when BSA was covaried.

A major, heretofore unrecognized, difference in these normotensive healthy children was the lower CI in the black children during preexercise, maximum exercise, and both recovery stages. The reduced CI was accompanied by longer time to peak ejection and lower change in velocity divided by change in time in the black males at peak exercise. All of these data are consistent with the increased SVR measured in the blacks and may indicate an increase in afterload when compared with their white counterparts.

Although high SVR has been implicated in the pathogenesis of essential hypertension in blacks,[21] we know of no data involving measurement of SVR response to stress in a biracial sample of healthy normotensive children. A potential explanation for these stress-induced SVR differences includes racial differences in reactivity to both psychological and physical components of the exercise test. Despite efforts to provide an unintimidating, nonthreatening environment for this study, the boys were

naked to the waist in a laboratory environment with predominantly white laboratory personnel applying electrodes and operating noisy equipment. There was some element of psychological stress prior to the formal onset of the exercise test, which may account for the preexercise racial differences in SVR as well as other preexercise differences. Other authors have found that compared with whites, blacks show greater BP response to psychological stress, including the mere presence of laboratory personnel,[8] and mental stress.[4] In these studies, SVR was not assessed.

Differences in SVR may relate to sexual maturation. The black boys, although matched for age with the white boys, were slightly larger and could have been more sexually mature. Tanner staging was not done on these boys and it is recognized that BP and presumably SVR may increase with increasing size and sexual maturation. Recent findings of 12- to 17-year old black and white males, however, showed no significant racial differences in pubic hair or genital stage in that age range other than slightly more advanced genital stage in 13-year-old white boys.[22] It is, therefore, highly unlikely that these prepubescent black children were statistically sexually more advanced than their white counterparts.

It has been postulated that the pathogenic process of essential hypertension may involve increased cardiac output during the borderline phase[21] and that the elevated cardiac output triggers an increased SVR that subsequently reduces cardiac output to normal values by the time essential hypertension is established. Schieken et al[23] demonstrated lower cardiac output and higher SVR at rest with increasing age in a predominantly white population of children. They stated that their observations lent some support to the "evolution of a hyperkinetic circulation in younger children at all levels of BP to a circulation with a higher SVR in older children." If this is true, it is remarkable that there is already reduced CI in the healthy normotensive 10-year-old blacks in our study. The implication is that these changes occur very early in blacks.

Falkner[9] theorizes that primary hypertension in blacks is predominantly a function of increased cardiovascular reactivity and associated increases in SVR. Our population of apparently healthy black boys may already be manifesting previously unmeasured reactivity differences in SVR and CI to the physical stressor of the preexercise and exercise conditions. The fact that SVR and CI differences were present in the preexercise state may indicate either that there are intrinsic differences at rest or that anticipation of the exercise test prompted an emotional stress that resulted in preexercise racial differences in reactivity.

Future studies in biracial populations should address the underlying hemodynamic regulators of BP at rest and during both psychological and physical stress. By measuring CI, BP, and SVR in both resting and stress conditions, one may identify markers or mechanisms intrinsic in the development of essential hypertension.

This research was supported in part by funds from the National Heart, Lung and Blood Institute, Bethesda, Md (HL 35073).

The authors wish to express their gratitude to Tonya Gardner for secretarial assistance, Bonnie Hadden and Gail Dicks for technical assistance, and Thomas Rhodes for technical and statistical support.

References

1. National Health Survey: Blood pressure of persons 18-74 years in the United States 1971-1972 (Vital and Health Statistics, series 2:150). Hyattsville, Md, National Center for Health Statistics, 1975.

2. Vital Statistics of the United States, 1973 (vol 2: Mortality Pathology). Hyattsville, Md, National Center for Health Statistics, 1977.

3. Dimsdale JE, Graham RM, Ziegler MG, et al: Age, race, diagnosis and sodium effects on the pressor response to infused norepinephrine. *Hypertension* 1987;10:564-569.

4. Murphy JK, Alpert BS, Moes DM, et al: Race and cardiovascular reactivity: A neglected relationship. *Hypertension* 1986;8:1075-1083.

5. Anderson NB, Lane JD, Muranaka M, et al: Racial differences in blood pressure and forearm vascular responses to cold face stimulus. *Psychosom Med* 1988;50:57-63.

6. Alpert BS, Flood NL, Strong WB, et al: Responses to ergometer exercise in a healthy biracial population of children. *J Pediatr* 1982;101:538-545.

7. Alpert BS, Dover EV, Booker DL, et al: Blood pressure response to dynamic exercise in healthy children—black vs white. *J Pediatr* 1981;99:556.

8. Light KC, Obrist PA, Sherwood A, et al: Effects of race and marginally elevated blood pressure responses to stress. *Hypertension* 1987;10:555-563.

9. Falkner B: Is there black hypertension? *Hypertension* 1987;10:551-553.

10. Guyton AC: Physics of blood, blood flow and pressure: Hemodynamics, in *Textbook of Medical Physiology*, ed 7. Philadelphia, WB Saunders Co, 1986, p 208.

11. Berman RE, Vaughn VC (eds): *Textbook of Pediatrics*, ed 12. Philadelphia, WB Saunders Co, 1979, p 1814.

12. Vaughn VC, McKay RJ (eds): *Nelson Textbook of Pediatrics*, ed 10. Philadelphia, WB Saunders Co, 1975, p 43.

13. Report of the second task force on blood pressure control in children: 1987 task force on blood pressure control in children from the National Heart, Lung and Blood Institute, Bethesda, Md. *Pediatrics* 1987;79:1-25.

14. Gardin JM, Kozlowski J, Dabestani A, et al: Studies of Doppler aortic flow velocity during supine bicycle exercise. *Am J Cardiol* 1986;57:327-332.

15. Marx GR, Hicks RW, Allen HD, et al: Measurement of cardiac output and exercise factor by pulsed Doppler echocardiography during supine bicycle ergometry in normal adolescent boys. *J Am Coll Cardiol* 1987;10:430-434.

16. Daley PJ, Sagar KB, Wann LS: Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise. *Br Heart J* 1985;54:562-567.

17. Alpert BS, Flood NL, Balfour IC, et al: Automated blood pressure measurement during ergometer exercise in children. *Cathet Cardiovasc Diagn* 1982;8:525-533.

18. Reinaj JT, Hsieh KS, Elixson M, et al: Cardiac output estimates in the pediatric intensive care unit using a continuous-wave Doppler computer: Validation and limitations of the technique. *Am Heart J* 1986;112:97-102.

19. Elkayam V, Gardin J, Berkley R, et al: The use of Doppler flow velocity measurement to assess the hemodynamic response to vasodilators in patients with heart failure. *Circulation* 1982;67:377-382.

20. Cumming GR: Hemodynamics of supine bicycle exercise in 'normal' children. *Am Heart J* 1977;93:617-622.

21. Guyton AC, Coleman TG: Quantitative analysis of the pathophysiology of hypertension. *Circ Res* 1969;24(suppl):1-19.

22. Harlan WR, Grillo GP, Cornoni-Huntley J, et al: Secondary sex characteristics of boys 12 to 17 years of age: The United States healthy examination survey. *J Pediatr* 1979;95:293-297.

23. Schieken RM, Clarke WR, Lauer RM: The cardiovascular response to exercise in children across blood pressure distribution. *Hypertension* 1983;5:71-78.

Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia
Barbara Starfield, MD, Baltimore
Larrie W. Greenberg, MD, Baltimore

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*What happens to the primary care graduates from your pediatric residency? Results presented in this article show that experience from Boston University. A surprisingly high degree of early career stability is reflected. This should provide a stimulus for us to evaluate the results of our programs.*—H.D.A.

Residency Training in General Pediatrics

Career Direction of Primary Care Graduates

Owen R. Mathieu, Jr, MD; Joel J. Alpert, MD; Stephen I. Pelton, MD

Residencies in primary care pediatrics have been developed as part of a national effort to educate pediatricians as generalists. Incentives provided by the federal government through Title VII, Section 784 of the Public Health Service Act (P.L. 94-484) have also provided support for residency training in family practice and general internal medicine.

Two assumptions have been made in developing these residencies. First, the programs would offer training in general pediatrics, community health, psychosocial medicine, and the "new morbidity," categories presumed lacking in usual graduate medical education; and second, participation would influence residents to choose and to continue in primary care careers as generalists.

Career choice has been evaluated by tracking the graduates of primary care programs.[1-3] Such data have proven useful in evaluating the success of the federal effort, and have indicated that residents trained in federally funded primary care programs were pursuing careers in general medicine and/or general pediatrics.[1,3]

Career choice has also been evaluated by surveying residents' career plans during training and performing follow-up surveys at later career points.[4-6] These reports have demonstrated an initial high rate of interest in primary care, which was replaced by interest in careers in subspecialties by the time residents entered the medical marketplace.

Career stability is as important an issue as career choice. Do graduates of the federally funded programs continue with their careers in primary care, or are these physicians likely to leave for a subspecialty?[2] Career stability among graduates of the federally funded programs has been reported in internal medicine.

Herein we report on careers of 11 cohorts of pediatricians who completed at least two years of general pediatric training at the Boston City Hospital (BCH)/Boston University School of Medicine program. These data suggest not only a preference for careers in general pediatrics but also a high degree of career stability.

THE PEDIATRIC PRIMARY CARE PROGRAM AT THE BCH

A pediatric primary care program has been developed at the BCH, and was established in 1974. The BCH is a 454-bed municipal teaching hospital serving largely lower-income inner-city residents. The hospital is surrounded by census tracts that have been designated Health Manpower Shortage Areas and are areas of high medical risk.

The pediatric service consists of an inpatient unit of 45 beds (with 2200 annual admissions) and a 48-bassinet nursery (1900 deliveries) that includes a 14-bed newborn intensive care nursery. One third of the infants delivered at the BCH receive long-term care at the Pediatric Primary Care Center. There are 13 000 yearly patient visits to primary care pediatric and adolescent services, including scheduled and unscheduled visits. There is a pediatric emergency department as well that receives an additional 25 000 emergency visits per year.

The goals of the pediatric residency are as follows: educating pediatricians for roles as generalists, especially in the inner city; training pediatricians to provide care along with nonphysician team members; expanding the age-range experience of pediatricians to include adolescent and young adult patients; and developing a curriculum in psychosocial pediatrics. The program has been supported by the Public Health Service and the Robert Wood

Accepted for publication Aug 23, 1988.
From the Department of Pediatrics (Drs Mathieu, Alpert and Pelton), Boston City Hospital, Boston University School of Medicine.
Reprint requests to Ambulatory Pediatrics, Boston City Hospital, 818 Harrison Ave, Boston, MA 02118 (Dr Mathieu).

Johnson Foundation, and has changed the educational direction of the department.

From 1974 until 1979, the program had a primary care track and a traditional track and was a joint cooperative program with the Department of Internal Medicine. From 1974 to 1979 the primary care trainee held his or her continuity session either in the hospital at a family-oriented primary care center or in a multiservice neighborhood health center. The traditional track trainee held his or her continuity session only in the hospital in the pediatric outpatient department. In the primary care pathway there was an interdisciplinary faculty consisting of pediatricians, internists, social scientists, nurse practitioners, social workers, and psychiatrists. The traditional track residents were exposed primarily to pediatric faculty only. In the traditional track continuity clinic, each resident was responsible for a panel of patients who usually received care from the emergency department in the physician's absence. At the primary care sites, senior faculty members, other resident team members, or nurse-practitioners provided coverage in the resident's absence.

In the primary care program continuity clinic-experience increased in the PL2 and PL3 years and totalled at least 25% of total training time over the three years of residency, while the traditional track residents continued with a single weekly session 10% for three years (Table 1).

The primary care trainees were presented a curriculum that exposed them to community issues; mental health, public health, and psychosocial concerns; and the new morbidity in pediatrics. The following activities were included: (1) a social science curriculum taught by anthropologists, epidemiologists, lawyers, and ethicists; (2) a child development program consisting of lectures, seminars, and consultations; (3) a supervised day-care experience for the observation of normal children; (4) a school health program in which residents serve as pediatricians for schools in the Boston Public School system; (5) an adolescent medicine program in which residents provide continuity in the adolescent primary care center; and (6) a well-newborn nursery rotation.

Table 1.—Comparison of Primary Care and Traditional Tracks

Feature	Primary Care	Traditional Track
Continuity, %	25	10
Location	Family center or neighborhood health center	Pediatric clinic
Faculty	Interdisciplinary	Pediatric
Unscheduled care	Faculty, nurses, house officer team on call	Emergency department

Table 2.—Response by Training Track

Training Track (y)	No. of Trainees	No. (%) of Respondents
Primary care (1974-1978)	29	25 (86.2)
Traditional track (1974-1978)	25	23 (92.0)
Primary care (1979-1984)	72	70 (97.2)
Total	**126**	**118** (93.7)

Table 3.—Careers by Training (1987) in All Training Tracks

	No. (%) of Subjects		
Training Track	Primary Care (1974-1978)	Traditional Track (1974-1978)	Primary Care (1979-1984)
Primary care			
Practice	11 (44)	9 (39.1)	46 (65.7)
Academic	8 (32)	3 (13)	4 (5.7)
Training	1 (4)	0 (0)	5 (7.1)
Total	20 (80)	12 (52.1)	55 (78.5)
Specialty			
Practice	1 (4)	7 (30.4)	2 (2.9)
Academic	3 (12)	1 (4.3)	4 (5.7)
Training	0 (0)	0 (0)	8 (11.4)
Total	4 (16)	8 (34.8)	14 (20)
Total other	1 (4)	3 (13)	1 (1.4)
Total	25 (100)	23 (100)	70 (100)

In 1979 the comparison phase of the program ended, and from 1979 to the present all pediatric residents at the BCH/Boston University School of Medicine have participated in the primary care program. In 1979, because of the large size and resulting scheduling problems in the pediatric and general medicine programs, they became separate training programs. Medicine at the BCH continued as a primary track (with approximately 30 residents) and pediatrics continued as a primary care program for all residents.

SUBJECTS AND METHODS

Since 1977, yearly questionnaires have been sent to program graduates that seek data on current professional activities (Table 2) and ask whether the pediatrician was in a primary care career or subspecialty field. Primary care careers were defined as general pediatric or adolescent office practice, hospital- or medical school–based practice, teaching, and administration in general pediatrics or public health. We asked whether the physician was in training or in practice at the time the questionnaire was completed. Those who reported having careers in the subspecialties also indicated whether they were in private practice, institutional practice, or training. With these data we compared reported careers of the 1974 to 1978 primary care cohorts, the 1974 to 1978 traditional track cohorts, and the 1979 to 1984 total primary care trainees.

RESULTS

From 1974 through 1984, 126 residents entered and spent at least two years of pediatric training at the BCH. As of 1987, information was current on 118 residents (93.7%). There was no significant difference in the response rate between cohorts (Table 2). Of the initial primary care cohorts

(1974 to 1978), 80% chose primary care careers, compared with 52% of the traditional track cohorts (Table 3). Sixteen percent of the primary care (1974 to 1978) cohorts reported themselves to be in subspecialty careers, compared with 34.8% of the traditional track (1974 to 1978) group. Of the single-track primary care cohorts (1979 to 1984), 18.5% were still in training, compared with 4% of the earlier (1974 to 1978) primary care cohorts and none of the traditional track cohorts. Of the 1979 to 1984 primary care cohorts, 78.5% were in general pediatrics and 20% had chosen subspecialty careers.

Career stability was judged by comparing career responses of the 1974 to 1979 entering cohorts in 1983 and 1987 (six to ten years after training). Only three of the 60 graduates had changed career direction during this period. All three graduates were trained in primary care. Two had gone into a primary care practice, having completed specialty training, while one had left primary care practice to enter specialty training.

COMMENT

Federal support for primary care training has been challenged, especially because of the predicted physician surplus. Congress asked for evidence of whether targeted support for primary care has influenced physicians' career choices. Positive outcomes have previously been reported for internal medicine.[3,5] Furthermore, Shelov et al[1] reported in 1987 that 75% of graduates of federally funded pediatric programs were pursuing careers in primary care practice in general pediatrics. Fifteen percent of those physicians in practice reported that they were practicing in hospitals or academic settings, and 8% were practicing in public health facilities. Graduates were two to five years past completion of training at the time. These data were based on a survey of program directors and provided valuable evidence in the budget debate.

Our study provides additional data that primary care programs have achieved the goal of educating pediatricians who pursue careers as generalists. Moreover, this survey reports that the 1974 to 1978 cohorts demonstrate early career stability and are continuing in general pediatrics. We do not know yet if this career stability will differ from an earlier American Academy of Pediatrics survey that reported that one third of practicing pediatricians between 40 and 75 years of age had made at least one career change, and that another 30% wanted to change at the time of the survey. Twenty-one percent had changed from general pediatrics to a specialty and 15% had changed to a salaried administrative position. One third of those pediatricians who had changed were already dissatisfied with their second career choice.[2]

In 1981, Crain et al[7] reported an increase in primary care practice among primary care pediatric trainees compared with traditional track trainees (62% vs 27%). Our survey adds to their report with a larger number of primary care–trained residents (95 vs 13). (The time interval between program completion and the survey was not specified by Crain and colleagues.[7])

We do not conclude that it was the BCH primary care program that influenced career choices. Residents chose the BCH program and were not randomly assigned during the 1974 to 1978 period. For the 1979 to 1984 cohorts, the residency had established its reputation as a primary care program.

We do suggest that the primary care program supports residents in their career choices, perhaps resulting in the reported career stability. The high rate of career stability may also have resulted from graduates of this program having more realistic expectations of their professional careers. A pediatrician principally trained in acute care medicine may not have similar expectations of a primary care practice career compared with a graduate of the programs such as those described herein.

Training in primary care is currently addressed to at least three different educational levels. Medical students, by elective or requirement, may be taught for extended periods in health clinics or primary care offices. Faculty training programs have been supported by not only the Public Health Service but also by private foundations such as the Robert Wood Johnson, Kellogg, and William T. Grant foundations. These fellowships carry various titles, but all train physicians to be scholars in general pediatrics. At the residency level, programs such as the one described in the present report have been offered at one time or another by approximately 25% of the pediatric residency programs in the United States.[8] The purposes of these training efforts are different. Medical students are given experience in getting to know patients over time, the fellowship programs produce scholars in the field, and the residency programs train physicians to pursue careers as generalist practitioners. Each of these efforts builds on the others.

Career choice is clearly not the only indicator of program effectiveness. The ultimate test of educational effectiveness may be whether physicians practice differently in an observable and measurable way, depending on the educational program. The original intention of the federal legislation was to increase access to primary health care services by increasing the number of primary care physicians. The present report suggests that the federal goal is being met. We believe, therefore, that our data support the use of targeted funding as a means of training physicians for careers in primary care.

This study was supported in part by Health Resource and Services Administration (Rockville, Md) grant D28-PE11108 and the Robert Wood Johnson Foundation, Princeton, NJ.

References

1. Shelov SP, Alpert JJ, Rayman I, et al: Federally supported primary care training programs and pediatric career. *AJDC* 1987;141:65-66.

2. American Academy of Pediatrics Committee on Expanding Pediatric Careers: Career in pediatrics. *Pediatrics* 1978;298:15-21.

3. Witzberg RA, Noble J: Career development among residents completing primary care and traditional residencies in medicine at the Boston City Hospital. *J Gen Intern Med* 1988;3:48-53.

4. Marienfeld RD: Comparison of initial house staff goals with eventual career plans in internal medicine. *J Med Educ* 1977;52:855-953.

5. Goldenberg DL, Pozen JT, Cohen A: The effect of a primary care pathway on internal medicine residents' career plans. *Ann Intern Med* 1979;91:271-274.

6. Benson MC, Linn L, Ward N, et al: Career orientation of medical and pediatric residents. *Med Care* 1985;23:1256-1264.

7. Crain LS, Dienst E, Mallory MJ: The effects of primary care vs traditional training or career choice in pediatrics. *West J Med* 1981;135:248-251.

8. Mathieu OR, Alpert JJ: Residency training in general pediatrics: The role of federal funding. *AJDC* 1987;141:754-757.

Connaught DTP Special Service

Dependable Delivery Service

Just dial toll-free
1-800-VACCINE
(1-800-822-2463)
from 8AM to 8PM

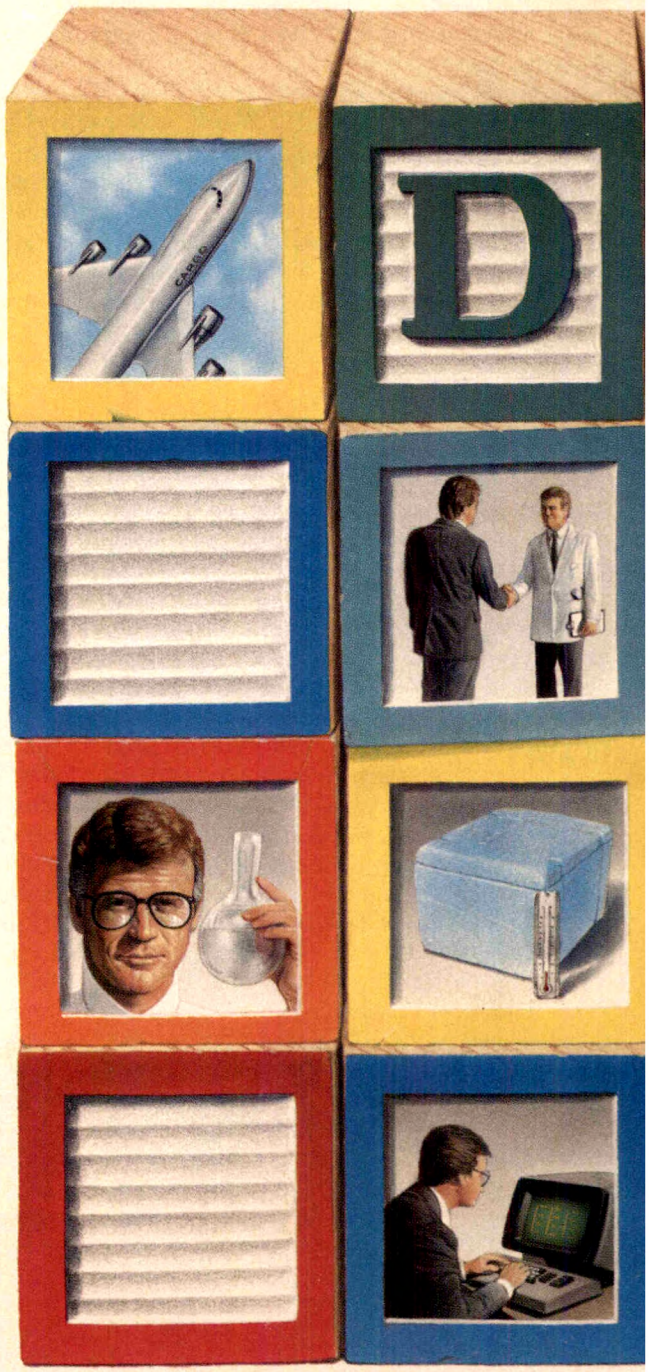
Temperature-controlled Shipping

Product integrity ensured
on a year-round basis
through special temperature
indicator and insulated
packaging

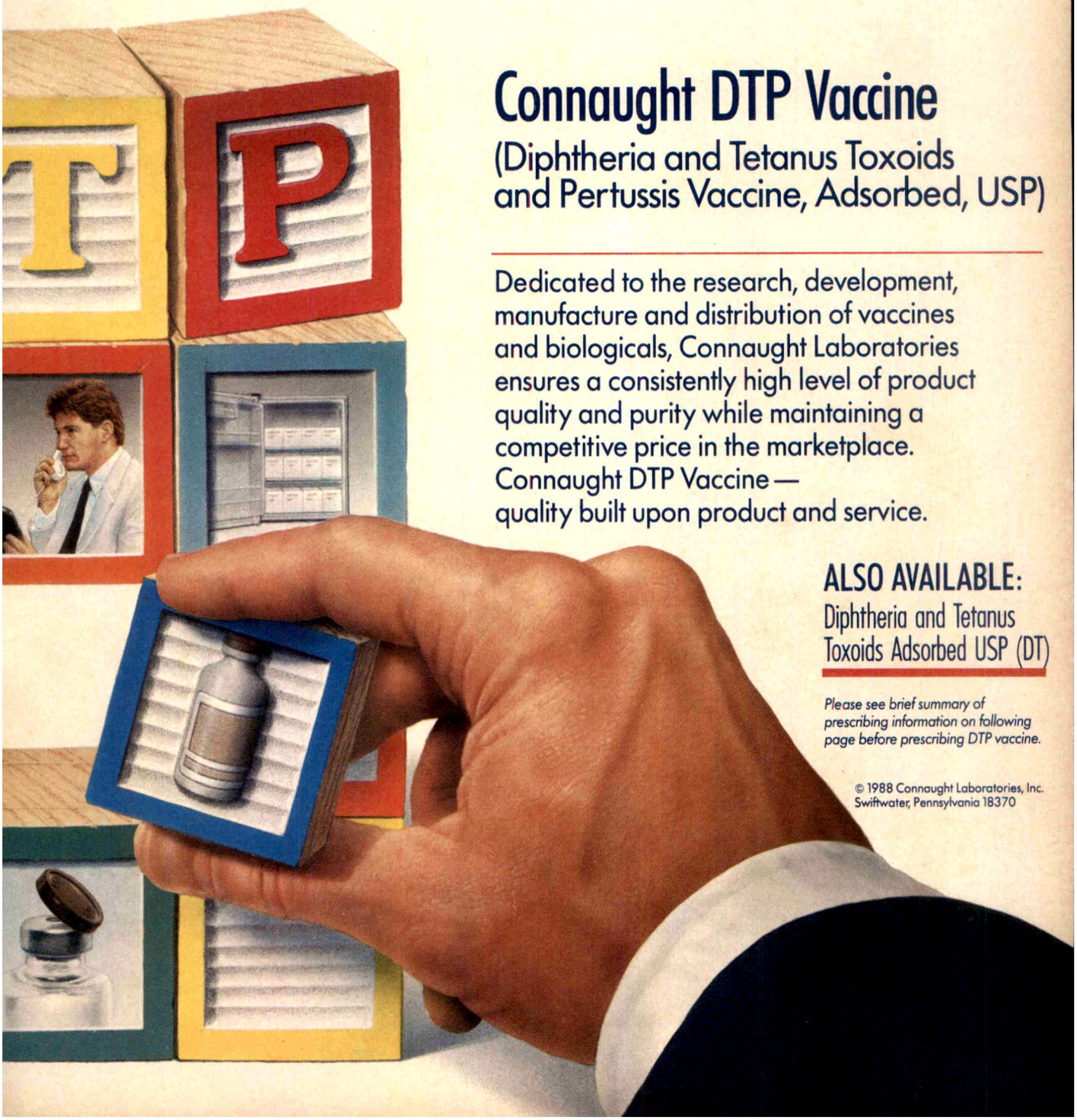
Physician Support Materials

Vaccine Monitoring Kit
to simplify compliance
with the National
Childhood Vaccine Injury Act

® CONNAUGHT LABORATORIES, INC.
Specialist in vaccines and biologicals



BUILDING BLOCKS FOR CHILDREN'S HEALTH



Connaught DTP Vaccine

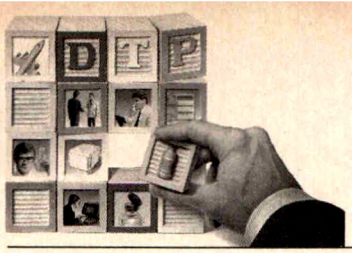
(Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, USP)

Dedicated to the research, development, manufacture and distribution of vaccines and biologicals, Connaught Laboratories ensures a consistently high level of product quality and purity while maintaining a competitive price in the marketplace. Connaught DTP Vaccine — quality built upon product and service.

ALSO AVAILABLE:
Diphtheria and Tetanus Toxoids Adsorbed USP (DT)

Please see brief summary of prescribing information on following page before prescribing DTP vaccine.

© 1988 Connaught Laboratories, Inc.
Swiftwater, Pennsylvania 18370



Connaught DTP Vaccine

(Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, USP)

BRIEF SUMMARY
Before prescribing, please consult the complete package circular.

INDICATIONS AND USAGE: For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping chough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS: *Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.*

Absolute contraindications.

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or local neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered an absolute contraindication to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.

WARNINGS: *This vaccine must NOT be used for immunizing persons 7 years of age and older.*

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS AN ABSOLUTE CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurological disorders, must be decided on an individual basis. Please refer to ACIP recommendations for the following categories of patients:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.**
2. **Infants and children with neurologic events temporally associated with DTP.**
3. **Incompletely immunized children with neurologic events occurring between doses.**
4. **Infants and children with stable neurologic conditions.**
5. **Children with resolved or corrected neurologic disorders.**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month, otherwise, the patient should be vaccinated while still on therapy.

Persons receiving immunosuppressive therapy, a recent injection of immune globulin, or having an immunodeficiency disorder, may not generate an adequate immunologic response to the DTP vaccine.

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Please refer to ACIP recommendations.

PRECAUTIONS

GENERAL

Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. However, these observations were not noted by Barkin, R.M., et al. Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics). Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.

TABLE 1. Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever >38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

*Number of adverse events per total number of doses regardless of dose number in DTP series.
†Occurring within 7 days of DTP immunization.

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent. If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS. It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2–6 months old and that approximately 85% of SIDS cases occur at ages 1–6 months, with the peak incidence occurring at 6 weeks–4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3–9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged.

The following illnesses have been reported as temporally associated with the vaccine; neurological complications including cochlear lesion, brachial plexus neuropathies, paralysis of the radial nerve, paralysis of the recurrent nerve, accommodation paresis, and EEG disturbances with encephalopathy. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.

Product information as of July, 1986

® CONNAUGHT® is a trademark owned by Connaught Laboratories, Inc.

Mfd. by: CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.
MKT0246 12/88
Printed in U.S.A. 0585

Articles

Mortality With Increasing Assisted Ventilation of Very-Low-Birth-Weight Infants

Lex W. Doyle, MB, BS; Laurence J. Murton MB, BS; William H. Kitchen, MD

• From Jan 1, 1977, to Jan 1, 1987, very-low-birth-weight (VLBW) infants consumed almost 90% of total patient-days of assisted ventilation of all infants born in one tertiary perinatal center. In the latter five years compared with the first five years, increasing resources allowed proportionately more VLBW infants to be offered assisted ventilation, and the patient-days of assisted ventilation consumed per live birth rose by almost 60%. All VLBW infants did not benefit equally from the increased assisted ventilation. Mortality in infants with birth weights below 1200 g decreased; unexpectedly, mortality in larger VLBW infants (birth weights, 1200 g to 1499 g) rose (relative odds, 3.11; 95% confidence intervals, 1.21 to 7.99). Despite the increased consumption of ventilator resources, there was no substantial impact on overall mortality in VLBW infants.

(*AJDC* 1989;143:223-227)

Mortality of very-low-birth-weight (VLBW) infants, those with birth weights from 500 g to 1499 g, has decreased in association with the advent of assisted ventilation,[1] which was not used extensively in our nursery until the middle 1970s. It is not clear, however, whether all VLBW infants have benefited equally from assisted ventilation. On one hand, not all have had equal access to assisted ventilation; in particular, infants below 800 g have had limited access in our nursery.[2] On the other hand, tiny infants are technically more complex and demanding, consuming disproportionately more ventilator resources.[3] It is possible that larger infants with a better prognosis may suffer if attention to their care is diverted as more and more tiny infants are offered intensive care, including assisted ventilation.

Data on in-hospital mortality and consumption of ventilator resources have been recorded prospectively on all infants with birth weights from 500 g to 1499 g born in our hospital from Jan 1, 1977, to Jan 1, 1987. During this time, ventilator resources in our hospital have doubled. The aim of our study was to determine whether the increased consumption of ventilator resources over the decade has affected mortality in inborn infants equally throughout the range of birth weights from 500 g to 1499 g, by comparing mortality in the first five years with that in the the second five years, within three birth weight subgroups: 500 g to 799 g, 800 g to 1199 g, and 1200 g to 1499 g. The birth weight subgroups in our study were chosen because originally we were inclined not to offer intensive care to all infants with birth weights less than 800 g,[2] a policy that has been relaxed because of the increased availability of ventilator resources; the subgroup of birth weights from 1200 g to 1499 g was selected to achieve balance, and for the same reason the time interval was halved.

PATIENTS AND METHODS

In the ten years from Jan 1, 1977, to Jan 1, 1987, there were 66 489 live births at the Royal Women's Hospital, Melbourne, the largest of the three tertiary (level 3) perinatal centers in the state of Victoria, with approximately 12% of all live births in the state during that time. The majority of infants were delivered to residents of Melbourne, situated close to sea level. Of the 66 489 live births, 1416 (2.1%) had birth weights from 500 g to 1499 g, inclusively; 57 (4.0%) died soon after birth because of lethal congenital malformations. The remaining 1359 VLBW infants born in our hospital were the subjects of our study. Excluded from this report are the 187 outborn VLBW infants admitted to our nursery over the same ten-year period.

Obstetric facilities at our hospital included ultrasound examination, hormonal tests of fetoplacental function, cardiotocography, tocolytic drugs for inhibition of premature labor, and antenatal steroid therapy to accelerate fetal lung maturation.[4] Delivery was by cesarean section for recognized maternal or fetal indications.[5] At least one pediatrician attended the delivery of infants with gestational ages of 24 weeks or more. An overhead radiant heater and facilities for active resuscitation were available. Only severely asphyxiated infants were intubated, and intermittent positive-pressure ventilation was continued beyond the delivery room only in infants who failed to establish satisfactory respiration. The policy was to transfer all infants with gestational ages of 24 weeks or more to the intensive care nursery for further assessment, but some infants died in the delivery room despite attempts at resuscitation. Ongoing assisted ventilation (either intermittent positive-pressure ventilation or continuous positive airway pressure) was provided via a nasotracheal tube, using infant ventilators. From Jan 1, 1977, to Jan 1, 1987, the facilities for assisted ventilation have increased at our hospital, the nominal ventilator capacity of the ten-cot intensive care nursery doubling from four to eight. Over the ten years, the same person has been ultimately responsible for the ongoing management of the intensive care nursery, including assisted ventilation. For all inborn VLBW infants, the total patient-days of assisted ventilation in the first five years were 2923, which almost doubled to 5655 in the second five years (Table 1). Aside from the increased resources for assisted ventilation, there have been no other major changes to management of VLBW infants in our hospital over the decade that were likely to have affected survival. In particular, we have had no oscillatory or high-frequency jet ventilators and no artificial surfactant. Other details of the antenatal and postnatal care of VLBW infants at our hospital have been published.[6]

Some infants who died were judged to be

Accepted for publication Aug 5, 1988.

From the Departments of Obstetrics and Gynaecology and Paediatrics, The University of Melbourne, Parkville (Drs Doyle and Kitchen), and The Royal Women's Hospital, Carlton (Dr Murton), Australia.

Reprint requests to the Department of Obstetrics and Gynaecology, The University of Melbourne, Parkville 3052, Australia (Dr Doyle).

Table 1.—Proportions Offered Intensive Care, Mortality, and Patient-Days of Assisted Ventilation for Very-Low-Birth-Weight Infants, Contrasting Inborn Livebirths During 1977-1981 With Those During 1982-1986*

	Birth Weight, g						Total 500-1499	
	500-799		800-1199		1200-1499			
	1977-1981 (n=122)	1982-1986 (n=145)	1977-1981 (n=254)	1982-1986 (n=324)	1977-1981 (n=234)	1982-1986 (n=280)	1977-1981 (n=610)	1982-1986 (n=749)
Infants Offered Intensive Care								
% of patients	34.4	46.9	94.5	99.7	100	100	84.6	89.6
No. of patients	42	68	240	323	234	280	516	671
Relative odds†	2.23 ($P=.005$)		16.96 ($P=.006$)		Not applicable		2.96 ($P=.001$)	
95% CI	1.28-3.91		2.22-129.7		. . .		1.78-4.94	
Mortality in All Infants								
% of patients	82.8	81.4	31.9	20.4	2.6	6.8	30.8	27.1
No. of patients	101	118	81	66	6	19	188	203
Relative odds†	0.79 (NS)		0.56 ($P=.004$)		3.11 ($P=.018$)		0.78 ($P=.14$, NS)	
95% CI	0.40-1.54		0.38-0.83		1.21-7.99		0.57-1.06	
Mortality Excluding Infants not Offered Intensive Care								
% of patients	50.0	60.3	27.9	20.1	2.6	6.8	18.2	18.6
No. of patients	21	41	67	65	6	19	94	125
Relative odds†	1.44 (NS)		0.65 ($P=.036$)		3.11 ($P=.018$)		0.95 ($P=.89$, NS)	
95% CI	0.65-3.18		0.43-0.97		1.21-7.99		0.68-1.31	
Patient-Days of Assisted Ventilation								
Total	941	1169	1445	3602	537	884	2923	5655
Per livebirth	7.71	8.06	5.69	11.12	2.29	3.16	4.79	7.55
Additional†	1.08 ($P=.61$, NS)		5.78 ($P<.0001$)		0.96 ($P=.23$, NS)		2.83 ($P=.0002$)	

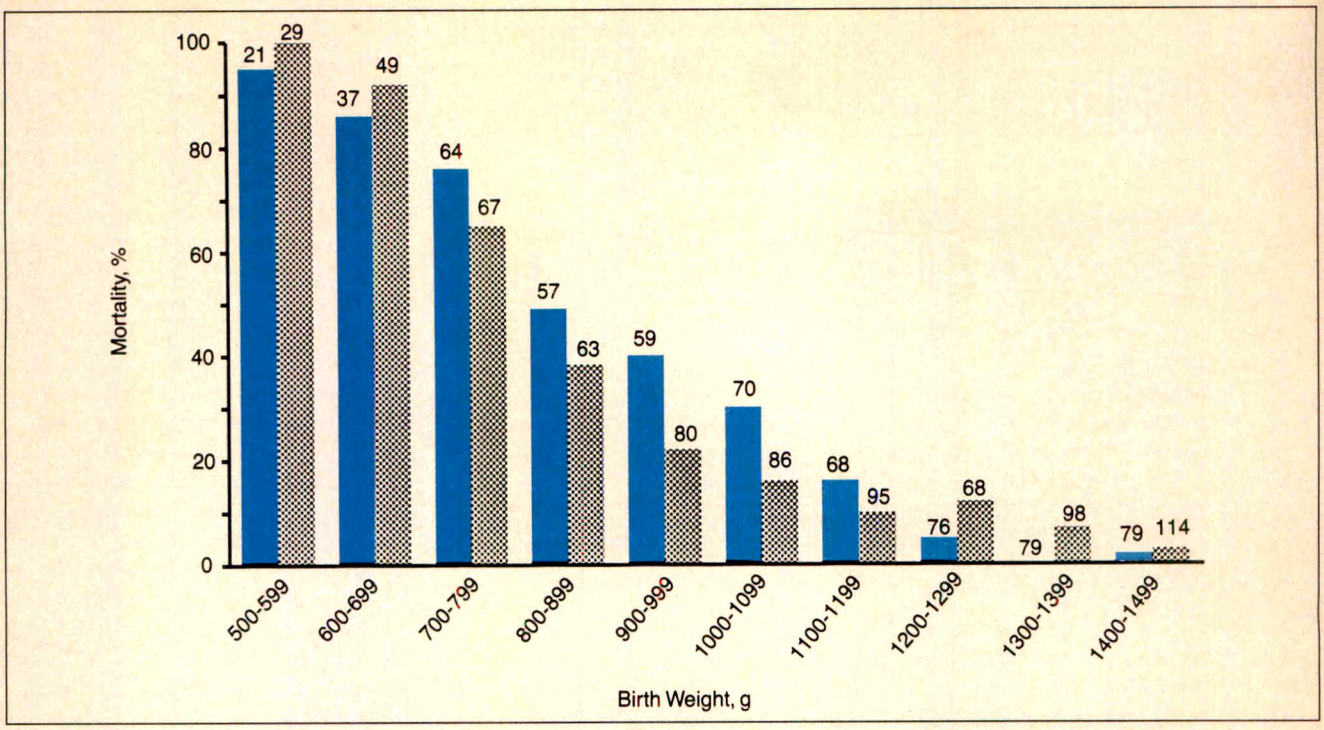
*CI indicates confidence interval; NS, not significant.
†In 1982-1986 compared with 1977-1981, adjusted for birth weight.

too immature to warrant intensive care, including assisted ventilation. The remaining infants were considered to have been offered intensive care; although not all VLBW infants required assisted ventilation or intensive care to survive, all are included in this report. Mortality comprised all deaths during the primary hospitalization, including delivery room deaths, infants beyond 28 days of age, infants transferred to other level 3 nurseries for ongoing care, and those not offered intensive care because they were thought to be too immature. The time each infant received assisted ventilation, if any, was recorded in days, part of a day counting as a whole.

Data on mortality and the consumption of ventilator resources were recorded prospectively. Because of the confounding influences of birth weight (and gestational age) on mortality and consumption of ventilator resources in VLBW infants, univariate analyses were largely avoided. Data were analyzed by multivariate techniques to adjust for changes in birth weight distribution over time, using logistic function regression for dichotomous outcome variables (mortality, proportions offered intensive care) and multiple linear regression for continuous outcome variables (patient-days of assisted ventilation). To test whether the consumption of ventilator resources and mortality had been affected equally over time, the study was divided into two eras of five years, 1977 to 1981 and 1982 to 1986, and three birth weight groups, 500 g to 799 g, 800 g to 1199 g, and 1200 g to 1499 g. For the whole cohort, and each birth weight subgroup, we calculated the relationship between era and the proportions of infants offered intensive care, mortality, mortality excluding those not offered intensive care, and the patient-days of assisted ventilation. Logistic function coefficients for era were used to estimate the relative odds of mortality, the relative proportions offered intensive care, and respective 95% confidence intervals. For the few univariate analyses, dichotomous variables were compared by χ^2 analysis, and continuous variables by a Student t test. For all statistical tests, $P<.05$ was considered to be statistically significant.

RESULTS

Of the 1359 VLBW infants born without lethal malformations, 391 (28.8%) died during their primary hospitalization. Comparing 1977 to 1981 with 1982 to 1986, overall mortality (unadjusted for birth weight) was similar and not significantly different ($\chi^2=2.1$, Table 1); the proportions of delivery room deaths (7.2% and 4.9%, respectively), deaths in the nursery during the first 28 days (22.5% and 20.2%, respectively), and deaths beyond 28 days (1.1% and 2.0%, respectively) were not significantly different between the two eras. From Jan 1, 1977, to Jan 1, 1987, infants with birth weights of 500 g to 1499 g consumed 89.4% of total patient-days of assisted ventilation for all infants born in our hospital. In the latter era, there were 22.8% more VLBW infants born without lethal malformations, yet consumption of patient-days of assisted ventilation was 93.5% higher (Table 1). For the whole cohort, increasing birth weight, as expected, was associated with decreased mortality ($P<<.0001$, Figure, Table 1) and increasing proportions of infants being offered intensive care ($P<<.0001$, Table 1). For the whole cohort, independent of the confounding influence of changes in birth weight distribution, intensive care was offered proportionately more often in the latter era (relative odds, 2.96; 95% confidence intervals, 1.78 to 4.94; $P<.001$; Table 1). Patient-days of assisted ventilation per live birth decreased with increasing birth weight



In-hospital mortality for inborn infants free from lethal malformations for two eras, 1977 to 1981 and 1982 to 1986, of ten-year study period in 100-g birth weight subgroups. Solid bars indicate 1977 to 1981; stippled bars, 1982 to 1986. Numbers at top of bars indicate numbers of infants.

(percentage of variance explained [R^2] = 2.9%; $P<.0001$), and, after adjusting for birth weight, increased significantly in the latter era by almost 60% (additional $R^2 = 1.0\%$; $P = .0002$; Table 1). Despite the increasing consumption of ventilator resources in the latter era, mortality was not significantly reduced, either for the whole cohort or for the subgroup offered intensive care (Table 1).

Infants With Birth Weights of 500 g to 799 g

Over the ten-year period, there were 267 infants born without lethal congenital malformations with birth weights from 500 g to 799 g; 157 (58.8%) were not offered intensive care and died soon after birth, 80 (65.6%) in the first five years and 77 (53.1%) in the second five years. Of the 110 live births offered intensive care, 62 (56.4%) died, 21 (50.0%) in the first five years and 41 (60.3%) in the second five years. Increasing birth weight was associated with decreased mortality ($P<.001$) and increasing proportions of infants being offered intensive care ($P<.001$). Independent of the confounding influence of birth weight, in the latter era more infants were offered intensive care (relative odds, 2.23; 95% confidence intervals, 1.28 to 3.91; $P = .005$). However, mortality was not significantly lower either in the whole birth weight subgroup or only in those offered intensive care (Table 1). Patient-days of assisted ventilation per live birth increased with rising birth weight ($R^2 = 7.3\%$; $P<.0001$) because more infants were offered intensive care as birth weight increased in this subgroup, but patient-days of assisted ventilation were not substantially different between the two eras (Table 1).

Infants With Birth Weights of 800 g to 1199 g

There were 578 infants born without lethal malformations and weighing 800 g to 1199 g; 15 (2.6%) were not offered intensive care and died soon after birth, 14 (5.5%) in the first five years of the study and only one (0.3%) in the latter five years. Increasing birth weight was associated with decreased mortality ($P<.001$) and increasing proportions of infants being offered intensive care ($P<.001$). Regardless of birth weight, proportionately more infants were offered intensive care in the latter era ($P = .006$, Table 1); mortality decreased overall ($P = .004$), and also in only those offered intensive care ($P = .036$, Table 1). Patient-days of assisted ventilation decreased with increasing birth weight ($R^2 = 3.7\%$; $P<.0001$). Adjusting for birth weight, each live birth from 1982 to 1986 consumed an extra 5.78 patient-days of assisted ventilation, more than double that of infants born from 1977 to 1981 (additional $R^2 = 3.3\%$; $P<.0001$; Table 1).

Infants With Birth Weights of 1200 g to 1499 g

There were 514 infants born without lethal malformations and weighing 1200 g to 1499 g; all were offered intensive care. Mortality decreased with increasing birth weight ($P = .006$). Unexpectedly, in contrast to the 800- to 1199-g birth weight subgroup, mortality was significantly higher in the latter era (1977 to 1981, 2.6%; 1982 to 1986, 6.8% [Table 1]; $\chi^2 = 4.0$; $P<.05$), and the difference remained after adjusting for birth weight (relative odds of mortality in 1982 to 1986, 3.11; 95% confidence intervals, 1.21 to 7.99; $P = .018$; Table 1). To investigate further why mortality should have increased over time in the subgroup with birth weights of 1200 g to

Table 2.—Selected Perinatal Variables and Their Contributions to In-Hospital Mortality in Inborn Infants With Birth Weights of 1200 to 1499 g, Contrasting Livebirths During 1977-1981 With Those Born During 1982-1986*

Perinatal Variable	Era 1977-1981 (n=234)	Era 1982-1986 (n=280)	Mortality† P
Gestational age, completed wk	30.5 (1.8)	30.4 (1.9)	.004
Birth weight, g	1347 (88)	1363 (87)	.20
Apgar score at 1 min	5.8 (2.3)	5.7 (2.2)	.64
Apgar score at 5 min	8.6 (1.6)	8.2 (1.7)	.48
Apgar score <4 at 1 min	40 (17.1)	43 (15.4)	. . .‡
Apgar score <6 at 5 min	11 (4.7)	15 (5.4)	. . .‡
Transfer in utero	99 (42.3)	101 (36.1)	.30
Male	146 (62.2)	143 (51.1)	.54

*Values are mean (SD) in first four rows and number (percent) in last four rows.
†Statistical significance of each variable in relationship to in-hospital mortality, determined by logistic function regression, the analysis including the effect of era of birth.
‡Not included in logistic regression analysis.

1499 g, infants in the two eras were compared for other potentially confounding perinatal variables (Table 2). There were no substantial differences between the two groups (Table 2), although infants born from 1982 to 1986 were relatively disadvantaged because their five-minute Apgar score was significantly lower ($t=2.24$; $P=.026$), but they were relatively advantaged because there were proportionately fewer males ($\chi^2=6.2$; $P<.02$). All of the variables in Table 2, along with the era of birth, were included in a logistic regression analysis, with mortality as the dependent variable. Adjusting for any or all of these variables had little effect on the significant association between increasing mortality and birth from 1982 to 1986 in the subgroup with birth weights of 1200 g to 1499 g. Adjusting for all variables listed in Table 2, only decreasing gestational age ($P=.004$) and being born in the latter era (relative odds, 3.12; 95% confidence intervals, 1.20 to 8.12; $P=.02$) were significantly associated with a higher mortality. The significant effect of decreasing birth weight disappeared when gestational age entered the analysis, and the Apgar scores, in utero transfers, and male sex were not significantly related to survival in these larger infants (Table 2).

The major cause of death in the infants with birth weights of 1200 g to 1499 g was hyaline membrane disease and its comorbidity. Cerebroventricular hemorrhage was implicated in two of six deaths in the first five years and in seven of the 19 deaths in the latter five years of the study. The diagnosis of cerebroventricular hemorrhage contributed to a decision to withdraw life-support systems from one infant in the first five years and two infants in the second five years of the study.

Patient-days of assisted ventilation per live birth in infants weighing 1200 g to 1499 g at birth were not significantly different between the two eras and were not related to birth weight (Table 1).

COMMENT

Over a ten-year period, VLBW infants consumed almost 90% of total patient-days of assisted ventilation of infants born in one tertiary perinatal center. In the latter five years (1982 to 1986), proportionately more VLBW infants were offered intensive care and although the use of assisted ventilation increased by 60% per live birth, overall mortality was not substantially reduced. The failure to significantly reduce overall mortality in the latter five years was partly attributable to the higher mortality of infants with birth weights of 1200 g to 1499 g, counterbalancing the gains in survival of infants with birth weights below 1200 g. Although patient-days of assisted ventilation per live birth increased in the latter era, it was infants with birth weights of 800 g to 1199 g who were largely responsible for the increase, and not infants with birth weights below 800 g. Furthermore, despite more infants with birth weights below 1200 g being offered intensive care in the latter era, survival improved only in those with birth weights of 800 g to 1199 g.

Gestational age and birth weight are important determinants of survival in VLBW infants, but they are strongly correlated; hence, when one is allowed for in a multivariate analysis, the other may become statistically insignificant. For infants weighing 1200 g to 1499 g at birth, because the birth weight range is so narrow, with the gestational age range unrestricted, it is not surprising that gestational age was statistically more significant with respect to mortality than birth weight. However, the observation that mortality was still significantly higher in the latter era after adjusting for all the variables in Table 2 means that the increased mortality from 1982 to 1986 in infants with birth weights of 1200 g to 1499 g was not related to increased admissions of higher-risk infants of less maturity or lower birth weight, or to imbalances in any of the potential prognostic variables in Table 2. The increased mortality also was not related to changes in attitude toward withdrawal of intensive care for infants with a poor long-term neurological prognosis.

It is uncertain whether the mortality of the larger VLBW infants (birth weights of 1200 g to 1499 g) increased in the second five years of the study solely because additional resources were directed to the smaller infants (birth weights below 1200 g). Other pressures on the nursery have included a 22.8% increase in admissions of inborn VLBW infants free of lethal malformations, including a 19.7% increase in those with birth weights from 1200 g to 1499 g. Moreover, there has been an increased consumption of ventilator resources by outborn infants; in the first five years, outborn VLBW infants consumed only 228 patient-days of assisted ventilation but this increased more than fivefold to 1163 patient-days of assisted ventilation in the latter era. Although the provision of ventilators and their use have increased over time, the staff required to maintain these facilities has not been increased at the same rate. Consequently, we speculate that as more ef-

fort has been expended with smaller VLBW infants and outborn infants, those with birth weights of 1200 g to 1499 g may have had problems overlooked, possibly to their detriment.

We have not attempted to include data on outborn VLBW infants admitted to our nursery during the study period because accurate mortality rates cannot be calculated for outborn infants as the number of VLBW infants not admitted to our hospital but kept at the hospital of birth is not known. Outborn VLBW infants were only 11.7% of all VLBW admissions to our nursery during the decade.

If the increased mortality in larger VLBW infants is true as more tiny VLBW infants are offered intensive care, and to a lesser extent as outborn infants consume more ventilator resources, it is clinically important. We speculate that the same phenomenon may have occurred in other centers. The only similar report[2] of which we are aware was in a comparison of mortality in VLBW infants born in 1977 and 1978 in two nurseries in Melbourne, one of which was our own. The other nursery, at the time, maintained a more aggressive policy toward tiny VLBW infants—proportionately more infants with birth weights below 800 g were offered intensive care. Mortality in that nursery for infants with birth weights below 800 g was significantly lower than in ours; on the other hand, mortality in their larger VLBW infants, particularly those with a birth weight above 1100 g, was significantly higher than ours.

Not all VLBW infants have benefited equally from the increased availability of resources for assisted ventilation over time; the gains in survival as more infants with birth weights below 1200 g have been offered assisted ventilation have been counterbalanced by the increased mortality of larger VLBW infants. It is important not to concentrate additional ventilator resources on extremely small and immature infants to the possible detriment of the greater number of heavier and more mature infants, who are easier to salvage, consume proportionately fewer resources per survivor, and have a better long-term prognosis.[7]

References

1. Kitchen WH, Rickards AL, Ryan MM, et al: Improved outcome to 2 years of very low birthweight infants: Fact or artifact? *Dev Med Child Neurol* 1986;28:579-588.
2. Bajuk B, Kitchen WH, Lissenden JV, et al: Perinatal factors affecting survival of very low birthweight infants: A study from two hospitals. *Aust Paediatr J* 1981;17:277-280.
3. Murton LJ, Doyle LW, Kitchen WH: Care of very low birthweight infants with limited neonatal intensive care resources. *Med J Aust* 1987;146: 78-81.
4. Doyle LW, Kitchen WH, Ford GW, et al: Effects of antenatal steroid therapy on mortality and morbidity in very low birth-weight infants. *J Pediatr* 1986;108:287-292.
5. Kitchen WH, Ford GW, Doyle LW, et al: Cesarean section or vaginal delivery at 24 to 28 weeks' gestation: Comparison of survival and neonatal and two-year morbidity. *Obstet Gynecol* 1985;66:149-157.
6. Kitchen WH, Yu VYH, Lissenden JV, et al: Collaborative study of very-low-birthweight infants: Techniques of perinatal care and mortality. *Lancet* 1982;1:1454-1457.
7. Doyle LW, Kitchen WH: Do neurological impairments and disabilities increase with decreasing gestational age in survivors of borderline viability at birth? *Aust Paediatr J* 1987;23:211-212.

In Other AMA Journals

JAMA

Estimated Prevalence of Anabolic Steroid Use Among Male High School Seniors

W. E. Buckley; C. E. Yesalis III; K. E. Friedl; W. A. Anderson; A. L. Streit; J. E. Wright (*JAMA* 1988;260:3441)

Pediatric Cyanide Intoxication and Death From an Acetonitrile-Containing Cosmetic

E. M. Caravati, T. L. Litovitz (*JAMA* 1988;260:3470)

Anabolic Steroid Use in Adolescence

W. V. Moore (*JAMA* 1988;260:3484)

Comparison of Airway Pathologic Lesions After High-Frequency Jet or Conventional Ventilation

Mark J. Polak, MD; William H. Donnelly, MD; Richard L. Bucciarelli, MD

• High-frequency jet ventilation in neonates has been associated with airway damage ranging from focal necrosis to complete airway obstruction with mucus and severe necrotizing tracheobronchitis. However, studies have lacked consistent criteria for assessment, and jet ventilation systems have varied widely. We compared autopsy and histopathologic findings in six neonates who died after prolonged jet ventilatory support with findings in six matched controls who died after receiving conventional ventilatory support. Jet ventilation consisted of a pressure-limited, time-cycled, flow-interrupter–type system. The airways of all patients were assessed by the histopathologic scoring system of Ophoven et al. No differences were observed between neonates who received jet ventilation or conventional ventilation. We believe that the risk of airway damage should not preclude the use of jet ventilation, although further monitoring is imperative.

(*AJDC* 1989;143:228-232)

High-frequency jet ventilation (HFJV) has become a valuable tool for the management of pulmonary interstitial emphysema and respiratory failure in neonates.[1-3] Along with reports of successfully treated infants, however, have been reports of infants with serious complications, including mucus obstruction of the trachea and necrotizing tracheobronchitis.[3-10]

The precise relationship between HFJV and necrotizing tracheobronchitis cannot be determined for a variety of reasons. First, necrotizing tracheobronchitis as a pathologic entity has not been clearly defined. Reported descriptions of the severity of this disease have ranged from focal ulcerations and squamous metaplasia to diffuse, deep necrosis and mucus obstruction of the large airways.[8-10] Second, only rarely have studies employed objective criteria for pathologic assessment.[10] Moreover, reports have covered the use of many different types of high-frequency ventilation systems.

The degree of airway damage reported elsewhere has not been noted in our experience with high-frequency ventilation. The present report compares histopathologic airway data from a group of infants who died after long-term (>90 hours) treatment with a jet ventilator with data from a group who died after treatment with conventional ventilation alone.

PATIENTS AND METHODS

The six infants in the present study were among 39 neonates treated with HFJV at Shands Hospital, University of Florida, Gainesville, between June 1984 and February 1988. Indications for jet ventilation were pulmonary interstitial emphysema, congenital diaphragmatic hernia, persistent pulmonary hypertension of the newborn, and respiratory failure that was unresponsive to conventional ventilation. All six infants received prolonged treatment (four to 15 days) with the jet ventilator. Their birth weights ranged from 480 to 1760 g, and their gestational ages ranged from 23 to 33 weeks (Table 1).

A single jet ventilation system was used for all patients—the Bunnell Life-Pulse Jet Ventilatory System (Bunnell Inc, Salt Lake City). The system is pressure-limited and time-cycled and employs a flow interrupter. In this system, the inflow jet of gas is regulated by an electronically controlled pinch valve. The inflow gas enters the airway 7 cm proximal to the tip of a commercially available endotracheal tube with a triple lumen (HiLo Jet Endotracheal Tube, National Catheter Corp, New York). Entrained gas, continuous positive airway pressure, and intermittent sigh breaths are provided by a conventional ventilator connected in parallel to the system through the central lumen of the endotracheal tube. The third lumen allows airway pressure monitoring at the tip of the endotracheal tube. A closed, servo-controlled humidification system provides approximately 100% relative humidity to the inflow gases.[11]

At autopsy, the airways of the six infants in the study had patchy areas of epithelial ulceration, squamous metaplasia, and no evidence of necrotizing tracheobronchitis. Consequently, we hypothesized that the pathologic changes in the airways of infants given ventilatory support with the high-frequency jet system did not differ from those of infants given ventilatory support by conventional methods. To test this hypothesis we selected a control group of neonates who died and underwent autopsy after treatment with conventional ventilators. We compared airway histopathologic characteristics of these infants with those of the six infants treated with HFJV.

A matched-control design was used; each of the six infants treated with jet ventilation was matched with an infant who had died during treatment with conventional ventilation (Table 1). In our nursery, conventional ventilatory support is provided by either a Baby Bird model 5900 infant ventilator (Bird Corp, Palm Springs, Calif) or a BP2001 Bear Cub infant ventilator (Bear Medical Systems, Riverside, Calif). The ventilation rate is generally 60 breaths per minute or less, and mean airway pressure is maintained at 12 cm H_2O or less. Oxygen is provided to maintain an arterial oxygen tension greater than 50 mm Hg. The ventilator rate and airway pressures are manipulated to keep the arterial oxygen tension at 40 to 45 mm Hg. Patients were matched as closely as possible for gestational age, birth weight, and total time of ventilatory support. To minimize the

Accepted for publication Oct 31, 1988.

From the Departments of Pediatrics (Drs Polak, Donnelly, and Bucciarelli) and Pathology (Dr Donnelly), University of Florida College of Medicine, Gainesville. Dr Polack is now with the West Virginia University School of Medicine.

Presented in part at the Southern Society for Pediatric Research, New Orleans, Jan 29, 1987, and the Society for Pediatric Research, Anaheim, Calif, May 8, 1987.

Reprints not available.

Comparison of Infants Receiving HFJV (J) With Their Matched Controls (C)*

Patient No./ Gestational Age, wk	Birth weight, g	Diagnosis	Cause of Death	Age at Death, d	Duration of Ventilation, d		Fio_2 ≥0.60, d		Average MAP, cm H_2O	
					Conventional	HFJV	Conventional	HFJV	Conventional	HFJV
J1/24	480	RI, hypotension	Renal failure	10	2	8	2	4	9	8.5
C1/27	650	RI	Pneumonitis	6	6	...	4	...	8	...
J2/25	680	RI	*Pseudomonas* pneumonia	83	68	15	15	15	12	15
C2/30	920	RDS	Necrotizing enterocolitis, *Pseudomonas* sepsis	75	36	...	28	...	8	...
J3/27	1000	RDS	Respiratory failure	36	32	4	7	4	10	14
C3/29	1000	RDS	Pneumonia	9	9	...	9	...	11	...
J4/33	1760	RDS	Respiratory failure	18	10	8	10	8	16	15
C4/32	1800	Nonspecific RDS	*Echovirus* hepatitis	20	10	...	0	...	6	...
J5/27	1180	RDS	Respiratory failure	9	1	8	1	8	16	13
C5/31	1530	Sepsis, pneumonia	Renal failure	16	16	...	16	...	16	...
J6/27	720	RI	Respiratory failure	8	2	6	2	6	9.5	14
C6/27	1100	Congenital syphilis	Respiratory failure	3	3	...	1	...	8	...

*HFJV indicates high-frequency jet ventilation; Fio_2, fraction of inspired oxygen; MAP, mean airway pressure; RI, respiratory insufficiency; and RDS, respiratory distress syndrome.

effects of changes in standards of neonatal care over time, each control infant was matched in birth date to within 12 months of the paired study infant.

After tissue sampling, the organ tissues from all perinatal autopsies routinely were stored for research purposes. The lungs were removed en bloc, perfused with 10% neutral buffered formaldehyde solution, and embedded in paraffin in a standard manner. Each block was marked with an autopsy number and a uniform site code number.

For our study, transverse sections from all blocks were cut from the midtrachea, the carina, and the right and left main bronchi. Slides were prepared by a standard protocol and stained with hematoxylin-eosin. All slides were identified by autopsy and site numbers. All autopsies, tissue sampling, and study examinations were supervised and reviewed by the same pathologist (W.H.D).

The histologic scoring system of Ophoven et al[12] was used to evaluate tissue sections. This four-point, nine-variable system records epithelial erosion, submucosal necrosis, polymorphonuclear leukocyte infiltration, surface cilia loss, intraepithelial mucus loss, presence of luminal mucus, hemorrhage, edema, and epithelial hyperplasia. In addition to providing a general injury score, the system identifies three patterns of injury by grouping related variables. Pattern I describes acute inflammation (erosion, necrosis, and polymorphonucleocyte infiltration). Pattern II describes derangement in cell composition and cell function (loss of cilia and intraepithelial mucus). Pattern III describes airway obstruction (presence of luminal mucus). Total injury scores and individual pattern scores from the six patients treated with jet ventilation and their matched controls were compared using the Wilcoxon rank-sum test.

RESULTS

The airways of all infants—those treated with the jet ventilator and those treated with the conventional ventilator—characteristically had patchy mucosal ulcerations and extensive squamous metaplasia. Many airways lacked ciliated epithelium and goblet cells. Luminal mucus accumulation was not a common finding, areas of hemorrhage were rare, and there were no cases of frank necrotizing tracheobronchitis (Fig 1). At all levels of the airways, the total injury scores from six infants who received HFJV did not differ from those of their six matched controls, nor were differences observed in patterns of injury, ie, inflammation (pattern I), derangement in cell composition and function (pattern II), and presence of extracellular mucus (pattern III) (Fig 2).

The pooled data are broken down into a comparison of total injury and pattern scores for each matched pair in Fig 3. It is apparent that there is a great deal of variability in scores that does not seem to be related to the size of the infant, type of ventilatory support, or duration of ventilatory support. For seven of the 12 patients, the nonspecific histologic variables of cellular edema and hyperplasia of surface epithelium (prominent in chronic rather than acute injury) accounted for a third or more of the total injury score at the level of both the trachea and carina.

COMMENT

Previously published reports have related jet ventilation to increased airway damage. Our histopathologic studies of airway specimens demonstrated no differences between infants treated with the jet ventilator and those who received conventional ventilatory support. Several factors may be responsible for the discrepancy in findings.

The first explanation may be related to differences in jet hardware. Our patients were treated with a single, standardized, production-ready jet ventilator system. Many investigators have reported the use of noncommercial, prototype jet ventilators.[3,4] Several of these systems have inadequate airway humidification, a problem implicated by investigators as a cause of jet ventilator–related damage.[13] Methods of humidification such as entrainment of humidified air and direct injection of water into the jet stream have been shown to be inadequate and dangerous in high-frequency systems other than low-flow oscillators.[11] The Bunnell jet-ventilation system humidifies inflow gases through a closed, servo-controlled pressure vessel in which water combines with the inflow gases in the vapor state. At body temperature, this system consistently delivers gas at virtually 100% relative humidity.[14]

Inappropriate placement of the jet in-

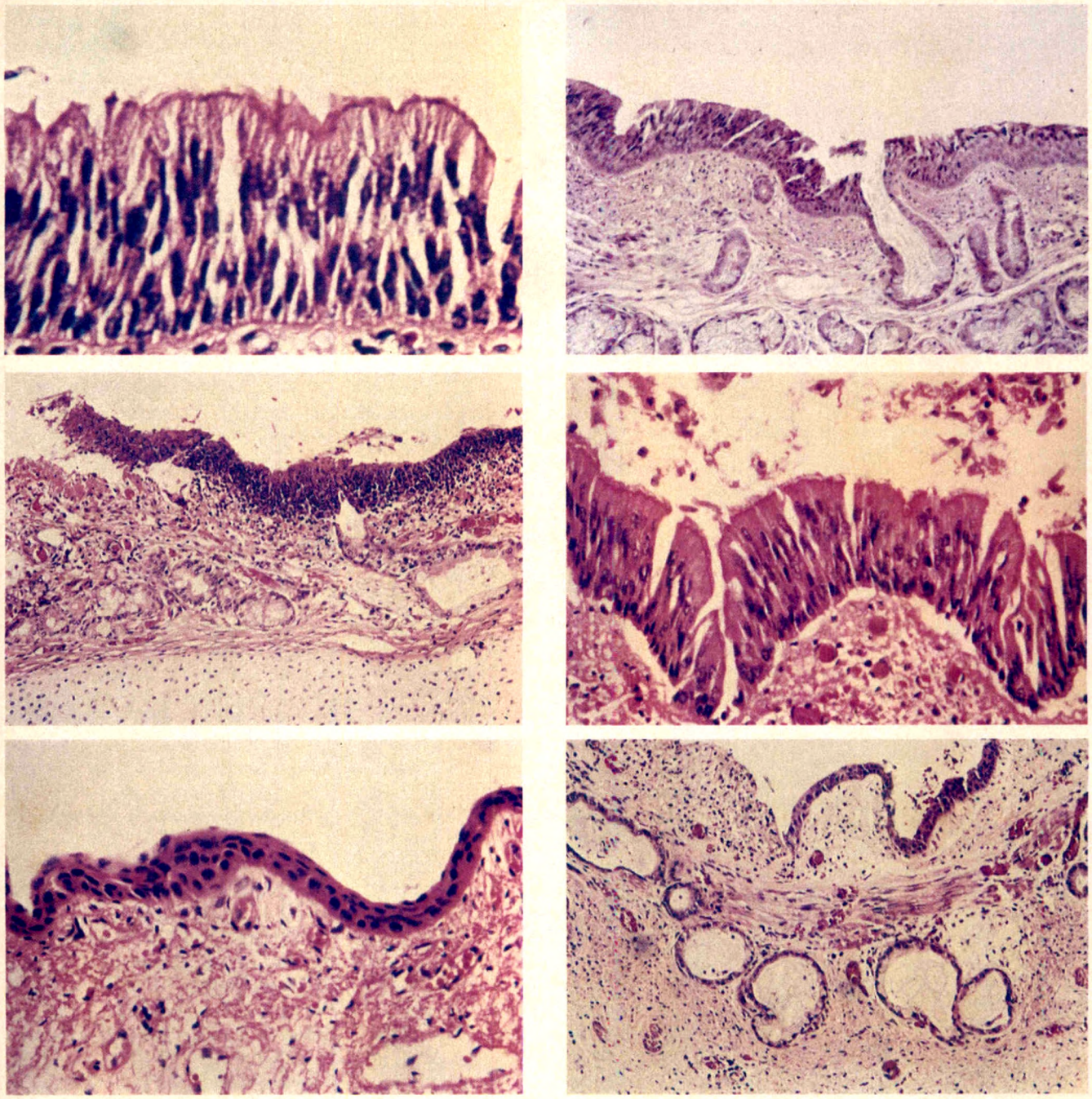


Fig 1.—Histologic features of tracheal sections from infants treated with jet (J) and conventional (C) ventilatory support. All sections were stained with hematoxylin-eosin. Top left, Section from C-5 demonstrates normal, ciliated, pseudostratified epithelium (original magnification, ×32). Top right, Section from C-1 shows transition from normal epithelium (left) to squamous metaplasia (right) (original magnification, ×6.3). Center left and right, Sections from J-4 showing acute damage with erosion, necrosis, and neutrophil infiltrations (original magnification, ×6.3) and normal epithelium with mucus and cellular debris in airway lumen (original magnification, ×16). Bottom left, Section from J-6 shows early squamous metaplasia with small cuboidal cells (original magnification ×6.3). Bottom right, Section from J-5 shows well-developed squamous metaplasia with extension into mucus glands (original magnification, ×6.3).

flow catheter may reduce efficiency in some systems. The position of this catheter has been shown to be of critical importance. Hamilton et al[15] demonstrated that the jet port must be positioned precisely 7 cm from the distal tip of the endotracheal tube to center the inflow jet of gas in the trachea with maximal entrainment of the bias gases. A difference of 1 to 2 mm, as can occur with a separate endotracheal tube and jet cannula configuration, disrupts airway dynamics and may lead to the formation of "jet lesions" on the trachea, as well as inadequate ventilatory function.

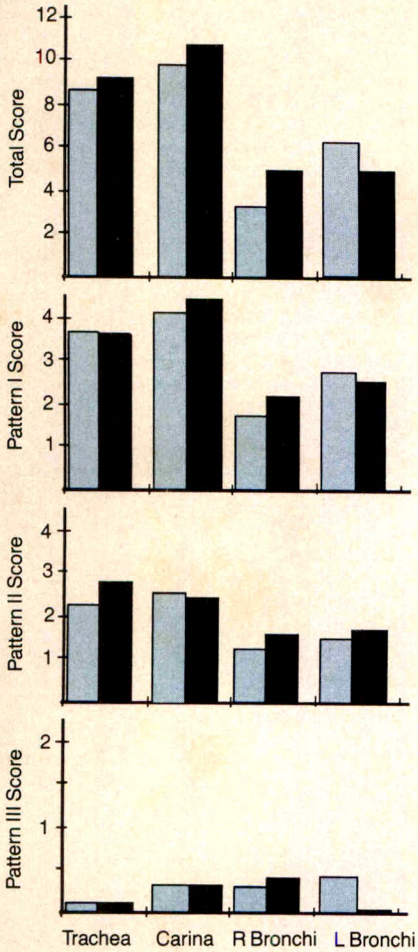


Fig 2.—Mean scores for tracheal histopathologic features in infants treated with jet (black bars; n=6) and conventional (white bars; n=6) ventilatory support. Scoring system of Ophoven et al[12] was used. Presented are total injury scores: pattern I (erosion, necrosis, and neutrophil infiltration); pattern II (loss of surface cilia, loss of intraepithelial mucus); and pattern III (luminal mucus). There were no significant differences when groups were compared by Wilcoxon rank-sum analysis.

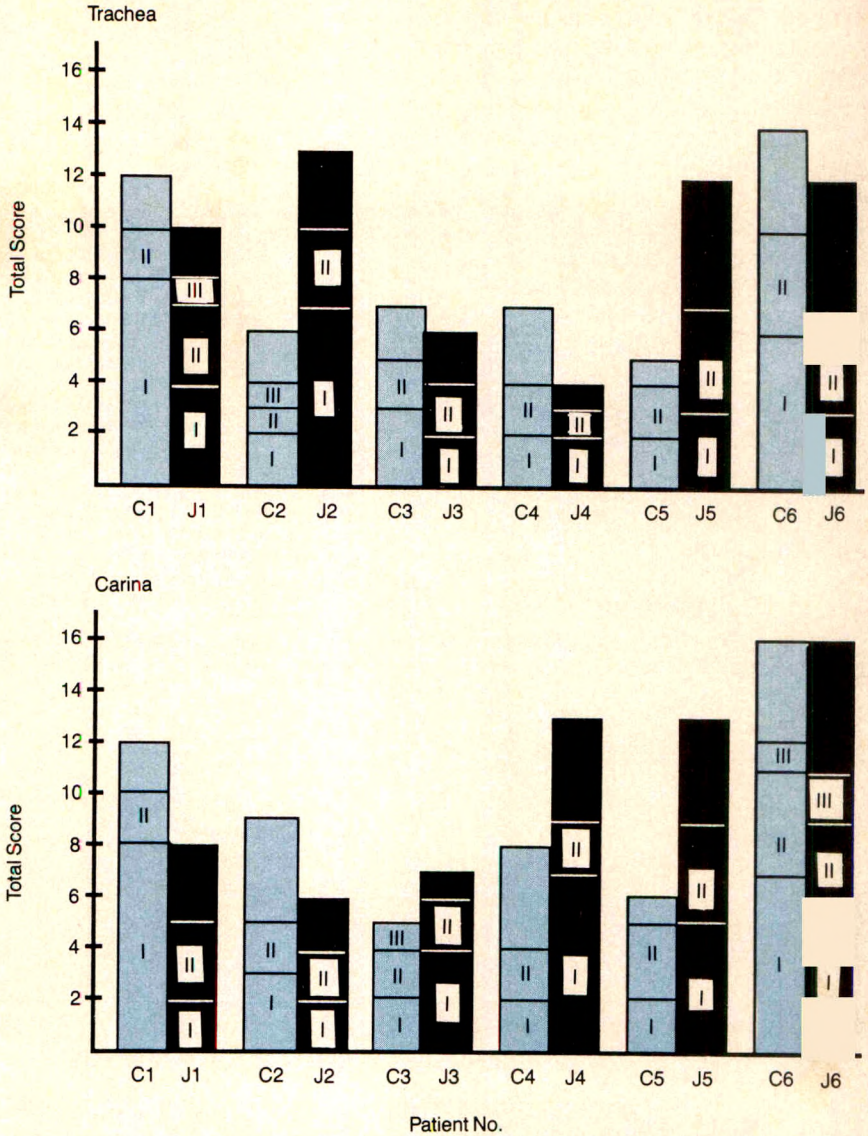


Fig 3.—Total scores from trachea and carina for each of 12 study infants. Score is sum of pattern I, II, and III scores and nonspecific features of hemorrhage, edema, and epithelial hyperplasia. C indicates conventional ventilatory support; J, jet ventilatory support.

We used a commercially available, triple-lumen endotracheal tube with a jet port placed exactly 7 cm from the tip of the endotracheal tube.

The finding of necrotizing tracheobronchitis in some studies and its absence in our six patients may be attributable to different durations of jet ventilation. Rasche and Kuhns[16] have suggested that conventional ventilator-induced airway damage is a function of the duration of ventilation. Little damage is observed within the first 72 hours, extensive tracheal necrosis occurs between 72 and 100 hours, and after 100 hours the predominant histopathologic change is squamous metaplasia, presumably representing the body's attempt to heal the acute damage.

Squamous metaplasia was an injury noted frequently in the airways of our patients who received HFJV or conventional ventilatory support. We believe that the airway damage induced by these two types of ventilatory support may differ early in the course of treatment. In all previously reported cases of necrotizing tracheobronchitis, jet ventilation was administered for less than 72 hours. These differences may disappear with prolonged ventilatory support. Consequently, after approximately 100 hours of continuous ventilatory support, the airways of all infants have a similar appearance. The injury patterns previously associated with short-term jet ventilatory support[8-10] may not be progressive and may not necessarily increase morbidity.

Another factor that must be considered is prolonged exposure to high concentrations of inspired oxygen. All of the HFJV-treated infants and four of six conventionally treated infants were exposed to high oxygen concentrations (fraction of inspired oxygen >0.60) for at least 75% of the total time that they

received mechanical ventilatory support. Hyperoxia has a well-established role in the development of pulmonary parenchymal damage,[17] and it has also been shown to have toxic effects on the epithelial lining of the conducting airways.[17,18]

The various jet ventilators, flow interrupters, oscillators, and their hybrids that are currently used in neonatal intensive care units differ widely in their mechanical properties and flow characteristics. As a result, the actual or potential damage produced in the airways and lungs of neonates is likely to vary substantially from one setting to another. For this reason, continued surveillance of the effects of HFJV on infants is imperative.

References

1. Boros SJ, Mammel MC, Coleman JM: Neonatal high frequency ventilation: Four years' experience. *Pediatrics* 1985;75:657-663.
2. Pagani G, Rezzonico R, Marina A: Trials of high-frequency jet ventilation in preterm infants with severe respiratory disease. *Acta Paediatr Scand* 1985;74:681-686.
3. Pokora T, Bing D, Mammel M, et al: Neonatal high-frequency ventilation. *Pediatrics* 1983;72: 27-32.
4. Carlon GC, Kahn RC, Howland WS, et al: Clinical experience with high frequency jet ventilation. *Crit Care Med* 1981;9:1-6.
5. Metlay LA, MacPherson TA, Doshi N, et al: A new iatrogenic lesion in newborns requiring assisted ventilation. *N Engl J Med* 1983;309:112-113.
6. Harris TR, Goochill WM, Wilson JF, et al: Necrotizing tracheobronchitis associated with high frequency jet ventilation in neonates. *Clin Res* 1984;132A:32.
7. Fox WW, Spitzer AR, Smith D, et al: Tracheal secretion impaction during hyperventilation for persistent pulmonary hypertension of the neonate. *Pediatr Res* 1984;323A:18.
8. Neu J, Hamilton L, Lineham J, et al: Long-term high-frequency jet ventilation in neonates. *Crit Care Med* 1984;12:833-835.
9. Kirpalani H, High T, Perluan M, et al: Diagnosis and therapy of necrotizing tracheobronchitis in ventilated neonates. *Crit Care Med* 1985;13: 792-797.
10. Boros SJ, Mammel MC, Lewallen PK, et al: Necrotizing tracheobronchitis: A complication of high-frequency ventilation. *J Pediatr* 1986;109: 95-100.
11. Bunnell JB: High-frequency hardware: Implementation of the latest mode of respiratory therapy. *Med Instrum* 1985;19:208-216.
12. Ophoven JP, Mammel M, Gordon MJ, et al: Tracheobronchial histopathology associated with high-frequency jet ventilation. *Crit Care Med* 1984;12:829-832.
13. Doyle HJ, Napolitano AE, Lippman HR, et al: Different humidification systems for high-frequency jet ventilation. *Crit Care Med* 1984;12: 815-819.
14. Chatburn RL, McClellan LD: A heat and humidification system for high-frequency jet ventilation. *Respir Care* 1982;27:1386-1391.
15. Hamilton LH, Londino JM, Linehan JH, et al: A pediatric endotracheal tube designed for high-frequency ventilation. *Crit Care Med* 1984; 12: 988-993.
16. Rasche RF, Kuhns LR: Histopathologic changes in airway mucosa of infants after endotracheal intubation. *Pediatrics* 1972;50:632-637.
17. Frank L: Effects of oxygen on the newborn. *Fed Proc* 1985;44:2328-2334.
18. Massaro GD, McCoy L, Massaro D: Hyperoxia reversibly suppresses development of bronchiolar epithelium. *Am J Phys* 1987;251:R1045-R1050.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Gastrointestinal Arterial Fibromuscular Dysplasia of Childhood
Shiro C. Imahori, MD (*Arch Pathol Lab Med* 1989;113:9-10)

Anaplasia in Solid Malignant Tumors of Childhood
Louis P. Dehner, MD (*Arch Pathol Lab Med* 1989;113:11-12)

Juvenile Granulosa Cell Tumors of the Ovary
Charles V. Biscotti MD, William R. Hart, MD (*Arch Pathol Lab Med* 1989;113:40-46)

Ganglioneuromatous Proliferation Associated With Juvenile Polyposis Coli
Bich N. Pham, MD, Rolando P. Villanueva, MD (*Arch Pathol Lab Med* 1989;113:91-94)

High-Frequency Jet Ventilation in Neonatal Pulmonary Hypertension

Waldemar A. Carlo, MD; Aris Beoglos, RN, MSN; Robert L. Chatburn, RRT; Michele C. Walsh, MD; Richard J. Martin, MD

• To determine if high-frequency jet ventilation is beneficial in neonates with persistent pulmonary hypertension, we compared the ventilator settings, blood gas concentrations, and outcome of infants who met established criteria for a high predictive mortality. During a six-year period, 14 neonates who had severe respiratory failure and hypoxemia while receiving conventional ventilation were treated with high-frequency jet ventilation. Twenty-three comparable infants meeting the same criteria were treated exclusively with conventional ventilation. After initiation of high-frequency jet ventilation there was a significant reduction in mean airway pressure and partial pressure of arterial carbon dioxide ($Paco_2$). In contrast, neonates treated exclusively with conventional ventilation continued to have higher airway pressures and $Paco_2$. However, there was no difference in the alveolar-to-arterial oxygen gradient, air leakage, incidence of bronchopulmonary dysplasia, or duration of assisted ventilation or oxygen supplementation. Furthermore, mortality was comparable in both groups of infants. These preliminary observations suggest that high-frequency jet ventilation can reduce airway pressure and $Paco_2$ in neonates with persistent pulmonary hypertension but does not appear to improve outcome.

(*AJDC* 1989;143:233-238)

Patients with respiratory failure and severe hypoxemia associated with persistent pulmonary hypertension of the neonate (PPHN) have a high mortality, despite maximal intensive therapy. Presently employed therapy combines ventilatory assistance with hyperventilation, vasodilators, and inotropic support.[1] An alternative treatment modality that has been developed for these patients is extracorporeal membrane oxygenation (ECMO),[2-4] which requires prolonged cardiopulmonary bypass and ligation of major blood vessels.

However, uncertainty exists regarding the potentially detrimental long-term side effects of ECMO, and thus the efficacy of less invasive alternative treatments should be evaluated in these patients. Furthermore, hemorrhagic complications and technical limitations currently require ECMO to be restricted to infants of at least 34 weeks' gestation and 2000-g birth weight.[3]

Hyperventilation may be beneficial in patients with PPHN as alkalosis can reduce pulmonary hypertension and extrapulmonary shunting.[1,5] High-frequency jet ventilation (HFJV), which has been employed safely in neonates with respiratory distress syndrome and pulmonary air leaks, consistently lowers the partial pressure of arterial carbon dioxide ($PaCO_2$) in these infants.[6,7] Thus, we hypothesized that HFJV would decrease $PaCO_2$ in patients with PPHN, resulting in improved oxygenation and outcome. Therefore, we reviewed our experience with HFJV in neonates with respiratory failure and severe hypoxemia who met previously published criteria predictive of a high mortality.[2,8]

PATIENTS AND METHODS

Patients

From 1982 to 1987 we used HFJV in 34 infants with birth weights of at least 2000 g and gestational ages of at least 34 weeks who developed severe respiratory failure. High-frequency jet ventilation was generally employed when mild hypocapnia ($PaCO_2$ <35 mm Hg) could not be achieved in neonates with severe hypoxemia despite peak inspiratory pressures greater than 40 cm H_2O. However, the attending neonatologist, in consultation with the parents, made the ultimate decision regarding the use of HFJV as a rescue treatment. Fourteen of these infants met both blood gas and ventilatory criteria frequently used to select neonates for ECMO[2,8] and they will be referred to as the HFJV group. These 14 infants had both an alveolar-arterial oxygen gradient ($AaDo_2$) greater than or equal to 610 mm Hg for eight consecutive hours averaged in four-hour epochs[8] and an oxygenation index greater than or equal to 40 for three of five blood gas measurements during the same period,[2] either of which would have predicted mortality of greater than or equal to 79%. Each criterion is used by various ECMO centers and the presence of both criteria was required to select the patients with the highest mortality. All 14 infants met these criteria before HFJV was initiated and all had evidence of extrapulmonary shunting and PPHN confirmed by one or more of the following means: echocardiographic evidence of right-to-left shunting at the atrial level; a preductal and postductal partial pressure of arterial oxygen (Pao_2) gradient of at least 40 mm Hg, and an increase in Pao_2 in response to hyperventilation of at least 40 mm Hg. The mortality rate was 40% in the 20 infants who did not meet the above blood gas criteria.

We compared the HFJV group with all infants (n=23) who met the same weight, gestational age, $AaDo_2$, and oxygenation index criteria and who only received conventional ventilation at our institution during the same six-year period. The groups were comparable on their main pulmonary diagnosis, other demographic data, and distribution over the study period (Table 1). Use of tolazoline, pancuronium bromide, sedatives (phenobarbital sodium, morphine sulfate), inotropic agents (dopamine hydrochloride, dobutamine hydrochloride), and sodium bicarbonate was also comparable in both groups. Four other infants who met all of the above criteria (two of whom had received HFJV) were excluded from this review because they were also treated with ECMO during the last three years of this series.

Accepted for publication Oct 3, 1988.

From the the Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland.

Reprint requests to Rainbow Babies and Children's Hospital, 2101 Adelbert Rd, Cleveland, OH 44106 (Dr Carlo).

Other patients not meeting all of the above criteria were either referred to other centers for ECMO during previous years or were treated in our institution with ECMO during the last year of the series.

All patients were initially treated with pressure-limited, time-cycled conventional ventilators. Hyperventilation was attempted by increasing peak inspiratory pressure and/or frequency with the conventional ventilators when severe hypoxemia was unresponsive to increases in the inspired oxygen concentration and ventilatory support. High-frequency jet ventilation was employed in the 14 infants only when severe hypoxemia was unresponsive to the described supportive measures and to conventional ventilation using very high peak inspiratory pressures.

Ventilators

Conventional ventilators used in these patients included the Bear BP200 (Bear Medical Industries Inc, Riverside, Calif), Bear Cub, and Sechrist (Sechrist Industries Inc, Medical Products Division, Anaheim, Calif), and their use was equally distributed in the two groups. Infants received ventilation at frequencies of less than 100 breaths per minute, although one infant in the HFJV group received higher frequencies with the conventional ventilator before HFJV was initiated. Peak inspiratory pressure during conventional ventilation was initially higher in the HFJV group than in the conventional ventilation group (Fig 1). Other ventilatory settings required during conventional ventilation were comparable between the two groups (Table 2, Fig 1).

The high-frequency jet ventilator employed in the present study has been previously described.[5] Briefly, it employs a solenoid valve to interrupt a high-pressure source and deliver small jets of gas. Airway pressures during HFJV were measured inside the distal endotracheal tube, as previously described and validated.[9] High-frequency jet ventilation was started at a mean of 80 ± 17 hours of age and was delivered at a mean frequency of 212 ± 29 breaths per minute, with an inspiratory-to-expiratory time ratio of 1:2.5 to 1:3. Selection of these ventilatory settings was based on previous animal and human research.[6,9] Pressure amplitude (peak inspiratory minus positive end-expiratory pressure) was used to control tidal volume and hence $Paco_2$. When the $Paco_2$ was unresponsive to pressure amplitude changes, frequency was slightly adjusted. Hyperventilation was attempted during HFJV to improve oxygenation. Changes in mean airway pressure and inspired oxygen concentration were also used to alter the Pao_2.

Table 1.—Clinical Data

Clinical Criteria	Ventilation Group* Conventional (N = 23)	High-Frequency Jet (N = 14)
Mean (± SEM) birth weight, kg	3.3 ± 0.1	3.3 ± 0.2
Mean (± SEM) gestational age, wk	38.9 ± 0.5	38.5 ± 0.6
Diagnoses, No. (%) of patients		
Meconium aspiration	13 (57)	6 (43)
Respiratory distress syndrome	5 (22)	4 (29)
Diaphragmatic hernia	3 (13)	2 (14)
Pneumonia	2 (9)	2 (14)
Sex, No. M/No. F	14/9	8/6
Race, No. W/No. B	12/11	10/4
Apgar score <7 at 5 min, % of patients	43	29
Drug therapy, % of patients		
Tolazoline hydrochloride	78	79
Pancuronium bromide	100	100
Dopamine/dobutamine	100/61	86/57
Phenobarbital/morphine	47/39	71/50
Sodium bicarbonate	83	64

*All $P<.02$.

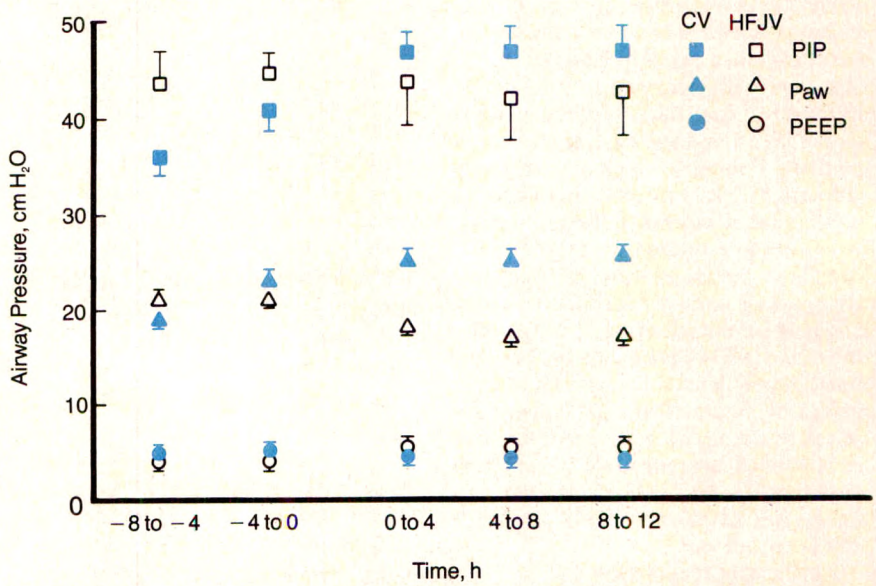


Fig 1.—Airway pressures in conventional ventilation (CV) and high-frequency jet ventilation (HFJV) groups during two 4-hour epochs when they met alveolar-arterial oxygen gradient and oxygenation index criteria and subsequent three 4-hour epochs. Infants in both groups were treated with CVduring two initial four-hour epochs. Increasing peak inspiratory (PIP) and mean airway pressures (Paw) were required in both groups during eight hours that criteria were being met; HFJV allowed reduction in mean airway pressure. PEEP indicates positive end-expiratory pressure; bars, mean ± SEM.

Data Analysis

Each postductal blood gas measurement as well as the corresponding mean airway pressure and inspired oxygen concentration was used in the calculation of the $AaDo_2$ and oxygenation index. The following equations were used in these calculations:

$$AaDo_2 = Fio_2(P_B - P_{H_2O}) - Paco_2 \times \{Fio_2 + [(1 - Fio_2)/R]\} - Pao_2$$

(where P_B indicates barometric pressure; P_{H_2O}, water vapor pressure [assumed to be 47 mm Hg]; and R, respiratory quotient [assumed to be 1.0])

$$\text{Oxygenation index} = Fio_2 \times (\text{mean airway pressure}/Pao_2) \times 100$$

Table 2.—Ventilatory Settings on Conventional Ventilation and Age When $AaDo_2$ and OI Criteria Were Met*

	Ventilation Group	
	Conventional	High-Frequency Jet
Mean (±SEM) ventilatory settings		
Fraction of inspired oxygen, %	100±0	100±0
Frequency, breaths/min	60±4	61±6
I-E ratio	1:1.1±0.1	1:1.2±0.1
Age, h		
Mean±SEM	27±4	64±14†
Median	19	55
Range	9-96	17-176

*$AaDo_2$ indicates alveolar-arterial oxygen gradient; OI, oxygenation index.
†$P<.05$; all other $P>.2$.

Table 3.—Outcome

	Ventilation Group*	
	Conventional	High-Frequency Jet
Mortality, % of patients	65	64
Air leaks, % of patients		
Before meeting criteria	35	57
After meeting criteria	35	14
Total	52	64
Survivors		
Bronchopulmonary dysplasia, % of patients (n/N)†	50 (4/8)	40 (2/5)
Assisted ventilation duration, d		
Median	15	13
Range	7-540	10-23
Oxygen supplementation duration, d		
Median	26	14
Range	10-540	13-57

*All $P>.2$.
†Numbers in parentheses indicate patients with bronchopulmonary dysplasia/all survivors.

The $AaDo_2$ was calculated for all blood gases and an average value was obtained for each four-hour epoch. Those infants with an $AaDo_2$ greater than or equal to 610 mm Hg for eight hours (two consecutive four-hour epochs) were considered to meet the $AaDo_2$ criterion.[8] Infants with blood gas and airway pressure data in which the oxygenation index was greater than or equal to 40 at three of five consecutive blood gas measurements during the same two 4-hour epochs met the oxygenation index criterion.[2] Infants ultimately selected for the review met both $AaDo_2$ and oxygenation index criteria.

Data are reported for the two 4-hour epochs when the $AaDo_2$ and oxygenation index criteria were being met (when all patients received conventional ventilatory support) and for the subsequent three 4-hour epochs (when patients were treated with HFJV or conventional ventilation). Other data collected included ventilatory settings, duration of assisted ventilation and oxygen supplementation, the incidence of air leaks (including pneumothorax, interstitial emphysema, pneumomediastinum, or pneumopericardium) and bronchopulmonary dysplasia, mortality, and postmortem results. In addition to the comparisons between the two study groups, the data were analyzed according to mortality. Categorical data were analyzed with the χ^2 and Fisher exact tests, while interval data were analyzed with paired and unpaired t tests. All results are given as the mean±SEM. A P value of less than .05 was required for statistical significance.

RESULTS

There was no difference in mortality, incidence of air leaks or bronchopulmonary dysplasia, and duration of assisted ventilation or oxygen supplementation between the HFJV and conventional ventilation groups (Table 3). During the two 4-hour epochs when the infants met the high mortality criteria, oxygenation was deteriorating, as evidenced by an increase in the $AaDo_2$ and oxygenation index in both groups (Fig 2). The $AaDo_2$ and oxygenation index did not differ between the groups during these epochs but criteria for high predictive mortality were met later in the HFJV group (64±14 hours vs 27±4 hours; $P<.05$; Table 2). Changes in the $AaDo_2$ during the subsequent three 4-hour epochs did not significantly differ between the two groups. However, the oxygenation index decreased during the first four-hour epoch of HFJV (53.4±3.4 to 42.1±5.6; $P<.05$) because of a reduction in mean airway pressure ($P<.05$, Fig 1) but did not change in the conventional ventilation group. The oxygenation index remained lower in the HFJV than in the conventional ventilation group throughout the three 4-hour epochs ($P<.05$). Data on six infants in the conventional ventilation group and five infants in the HFJV group are not given for the last one or two 4-hour epochs because of death (n=9) or crossover to conventional ventilation (n=2).

Between the first and second four-hour epoch, when all patients were treated with conventional ventilation, peak inspiratory pressure increased in both groups. Peak inspiratory pressure was higher in the group that subsequently received HFJV than in the conventional ventilation group during this time (44.7±1.5 cm H_2O vs 41.3±1.6 cm H_2O; $P<.05$; Fig 1). Mean airway and positive end-expiratory pressures did not differ between the two groups during these first two 4-hour epochs.

Initiation of HFJV decreased mean airway pressure (21.1±1.1 cm H_2O to 17.8±1.6 cm H_2O; $P<.05$) but did not alter peak inspiratory or positive end-expiratory pressures. In contrast, patients in the conventional ventilation group required further increases in peak inspiratory pressure (up to 47.4±2.2 cm H_2O; $P<.05$).

The $PaCO_2$ was higher in the HFJV group (35.6±3.1 mm Hg vs 32.0±1.9 mm Hg; $P<.05$) in the four-hour epoch that preceded initiation of HFJV and decreased after initiation of HFJV to levels lower than those in the conventional ventilation group ($P<.05$; Fig 3). In contrast, in the conventional ventilation group the $PaCO_2$ decreased between the first and second four-hour epochs,

when criteria were being met but did not subsequently change. Changes in pH reflected changes in $PaCO_2$, and pH increased with the initiation of HFJV ($P<.001$), remaining higher than in the conventional ventilation group throughout the last three 4-hour epochs. The total duration of HFJV was 69±23 hours.

Postmortem studies disclosed microscopic inflammatory changes of the trachea suggestive of mild necrotizing tracheobronchitis in one of seven infants in the HFJV group. None of the infants treated exclusively with conventional ventilation developed microscopic changes in the trachea. No macroscopic changes of necrotizing tracheobronchitis were observed in infants in either group. One infant in the conventional ventilation group who survived the initial hospitalization died at 540 days of age.

As mortality was not influenced by treatment modality we combined both groups to identify characteristics that might distinguish between survivors and nonsurvivors. Infants who survived more often were less mature and white, and usually had respiratory distress syndrome and pneumonia but not meconium aspiration (all $P<.05$; Table 4). However, logistic regression analysis showed that diagnosis was the strongest predictor of mortality ($P<.001$) and that gestational age and race did not add significantly to the prediction of mortality. Survivors also had a lower $AaDO_2$ and a higher $PaCO_2$ at the time the criteria were met. Infants who survived tended to be male, have an Apgar score greater than or equal to 7 at 5 minutes, require a lower ventilatory frequency, and have a lower oxygenation index than infants who died ($.05<P<.2$) (Table 4). Other data analyzed did not differ between the groups ($P>.2$).

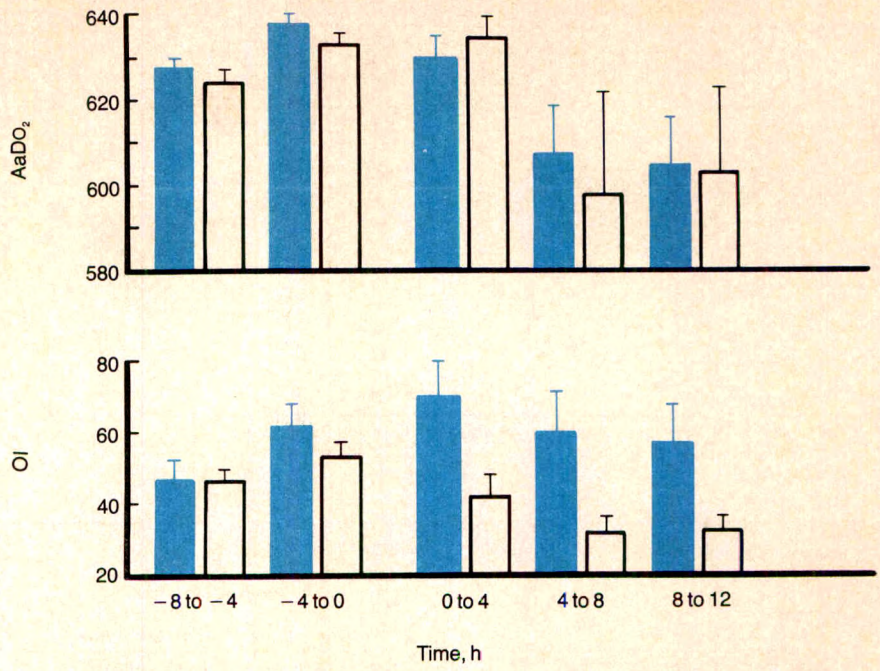


Fig 2.—Oxygenation index (OI) and alveolar-arterial oxygen gradient ($AaDO_2$) in conventional ventilation (black bars) and high-frequency jet ventilation (white bars) groups during same epochs as in Fig 1. In conventional ventilation group OI worsened from first to second four-hour epoch and did not improve with continuation of conventional ventilation. Use of high-frequency jet ventilation produced immediate improvement in OI that was sustained during subsequent three 4-hour epochs. Vertical bars indicate mean ± SEM.

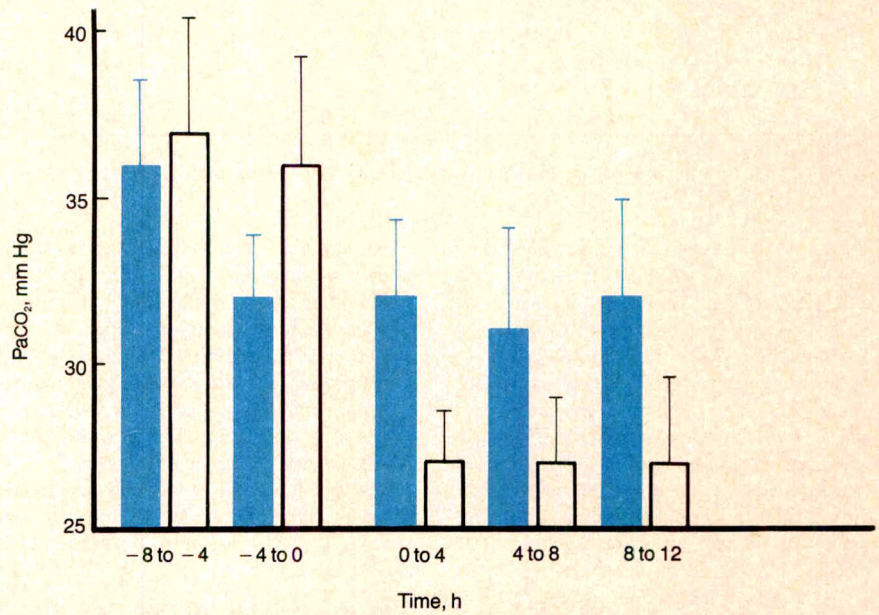


Fig 3.—Partial pressure of carbon dioxide ($PaCO_2$) in conventional ventilation (black bars) and high-frequency jet ventilation (white bars) groups during same epochs as in Figs 1 and 2. $PaCO_2$ decreased and remained low throughout subsequent three 4-hour epochs.

COMMENT

We have shown that in infants with PPHN, HFJV reduced mean airway pressures and improved CO_2 elimination when compared with infants treated with conventional ventilation. However, neither morbidity of assisted ventilation nor mortality was reduced by HFJV. These preliminary observations suggest that reduction of airway pressures and $PaCO_2$ by employing HFJV as rescue treatment in patients with PPHN does not improve outcome in this high-risk population.

Important limitations of this study should be acknowledged. High-frequency jet ventilation was used as a rescue application in these infants over a six-

Table 4.—Clinical Data and Ventilator Settings According to Survival			
	Survivors (N=13)	Nonsurvivors (N=24)	P
Mean (±SEM) gestational age, wk	37.2±0.5	39.5±0.5	.001
Diagnoses, No. (%) of patients			
Meconium aspiration	2 (15)	17 (71)	.001
Respiratory distress syndrome	7 (54)	2 (8)	.002
Pneumonia	3 (23)	1 (4)	.07
Diaphragmatic hernia	1 (8)	4 (28)	.10
Sex, No. M/No. F	10/3	12/12	.11
Race, No. W/No. B	11/2	11/13	.02
Apgar score <7 at 5 min, No. of patients	3	11	.17
Frequency, breaths/min	53±5	65±4	.09
Mean (±SEM) alveolar-arterial oxygen gradient, mm Hg	630±4	641±2	.02
Mean (±SEM) oxygenation index	52±5	62±5	.13
Mean (±SEM) partial pressure of arterial carbon dioxide, mm Hg	38±3	31±2	.04

year period and the group used for comparison was retrospectively selected from patients cared for during the same period. Other investigators have encountered difficulties in performing prospective controlled trials in patients with PPHN and a high predicted mortality.[3,4,10,11] Although both infant groups were treated during the same time period, we cannot assume that the selection of ventilatory treatment was unbiased. The sickest infants may have been selected for the HFJV group, as suggested by the higher peak inspiratory pressure and $PaCO_2$ during the period of conventional ventilation in the infants who were subsequently treated with HFJV. This may have limited our ability to detect a beneficial effect of HFJV. High-frequency jet ventilation was initiated at 80±17 hours of life and it is possible that, as previously suggested,[10] earlier use of HFJV may have resulted in better outcome in these patients. It should be stressed that the conclusions reached from this review are limited only to jet ventilation and to the ventilatory strategies employed. The study population was sufficient to detect a large (50%) reduction on any outcome variable with a power of 0.85; however, we would not have been able to detect smaller effects with only 37 patients. Finally, data on predicted mortality are critically dependent on multiple variables of patient care that vary between centers and with time. This is underscored by the fact that mortality in infants receiving HFJV or conventional ventilation was lower than expected from previous reports using either the $AaDO_2$ or oxygenation index criterion, even though our patients met both criteria. Furthermore, introduction of a new treatment such as HFJV may be accompanied by other subtle changes in clinical practice that may affect outcome.

Two previous reports on the use of high-frequency oscillatory ventilation in comparable patient populations suggested improved outcome.[10,12] Kohelet et al[12] treated 41 infants with PPHN and birth weight greater than 2.0 kg. High-frequency oscillatory ventilation improved oxygenation and CO_2 elimination despite a reduction in mean airway pressure. Furthermore, only five infants died. However, these investigators did not use accepted criteria for high predicted mortality. Cornish et al[10] used high-frequency oscillatory ventilation in 15 infants of at least 33 weeks of age who met ECMO criteria ($AaDO_2 \geq 600$ mm Hg for six hours [eight patients] or acute deterioration [seven patients]). Seven infants (only two of whom had met the $AaDO_2$ criterion) improved with high-frequency oscillatory ventilation and six of these patients ultimately survived without the need for ECMO. Infants who responded to high-frequency oscillatory ventilation tended to be those who qualified because of acute deterioration and they were smaller and more immature than those infants who ultimately required ECMO. We did not evaluate the effectiveness of HFJV in patients with acute deterioration and it is possible that such patients may benefit from this therapy. Furthermore, our patients were probably sicker than those previously reported as they had a higher $AaDO_2$ for a longer time and also met the oxygenation index criterion. Consistent with the findings of Cornish et al,[10] we found that the less mature infants were more likely to survive; this phenomenon appears to be disease related in part, as infants with respiratory distress syndrome rather than meconium aspiration tended to survive.

Bohn et al[13] used high-frequency oscillatory ventilation in 16 neonates with diaphragmatic hernia and severe hypoxemia. Both oxygenation and CO_2 elimination improved during high-frequency ventilation. However, despite the improved blood gas concentrations, only two patients ultimately survived. Other investigators[14-16] have successfully used various types of high-frequency ventilators as a rescue treatment in patients with PPHN, but the unavailability of criteria for impairment of oxygenation limits comparison with our data.

Extracorporeal membrane oxygenation has produced excellent survival statistics (approximately 90%) among patients with a high predicted mortality.[2-4] However, this therapy may be accompanied by short- and long-term complications such as hemispheric hypoxic-ischemic brain injury.[17] Thus, the evaluation of safer alternative therapies or improved ECMO techniques is necessary. It should be mentioned however, that controversy exists as to the mortality rate of infants with PPHN treated with conventional ventilation. For example, Wung et al[11] employed a well-designed clinical care protocol using conventional ventilation in 15 patients with PPHN and reported a 100% survival. It is possible that the improved outcome could result from particular strategies employed with conventional ventilation. Certainly, further evaluation of less invasive alternatives is necessary.

Animal models of PPHN have been difficult to develop. Models of meconium aspiration have been used in studies of high-frequency ventilation. In cats with experimentally induced meconium

aspiration, conventional ventilation produced better oxygenation than either HFJV or high-frequency positive-pressure ventilation.[18,19] In contrast, another animal study showed that HFJV maintained blood gas concentrations comparable to those encountered during conventional ventilation and allowed airway pressure to be decreased.[20] However, caution should be exercised when extrapolating these animal data to the clinical situation, as animal models do not strictly mimic the asphyxial insult that some meconium-stained infants undergo.

In summary, we have used HFJV as a rescue therapy in neonates with severe respiratory failure that is unresponsive to conventional ventilation. Oxygenation was maintained and CO_2 elimination was enhanced with HFJV, but there was no improvement in survival or short-term morbidity when compared with a group of infants who were treated with conventional ventilation. Although a large, prospective, controlled trial would be necessary to determine if high-frequency ventilation is superior to conventional ventilation in the treatment of these patients, our preliminary data suggest that HFJV, when used as a rescue treatment, may not provide consistent benefits and will not always preclude the need for ECMO or other alternative treatment modalities.

References

1. Fox WW, Duara S: Persistent pulmonary hypertension in the neonate: Diagnosis and management. *J Pediatr* 1983;103:505-514.
2. Bartlett RH, Gazzaniga AB, Toomasian J, et al: Extracorporeal membrane oxygenation (ECMO) in neonatal respiratory failure. *Ann Surg* 1986;204:236-244.
3. Bartlett RH, Roloff DW, Cornell RG, et al: Extracorporeal circulation in neonatal respiratory failure: A prospective study. *Pediatrics* 1985;76: 479-487.
4. Kirkpatrick BV, Krummel TM, Mueller DG, et al: Use of extracorporeal membrane oxygenation for respiratory failure in term infants. *Pediatrics* 1983;72:872-876.
5. Lyrene, RK, Welch KA, Godoy, G, et al: Alkalosis attenuates hypoxic pulmonary vasoconstriction in neonatal lambs. *Pediatr Res* 1985; 19:1268-1271.
6. Carlo WA, Chatburn RL, Martin RJ, et al: Decrease in airway pressure during high-frequency jet ventilation in infants with respiratory distress syndrome. *J Pediatr* 1984;104:101-107.
7. Pagani G, Rezzonico R, Marini A: Trials of high frequency jet ventilation in preterm infants with severe respiratory disease. *Acta Paediatr Scand* 1985;74:681-686.
8. Beck R, Anderson KD, Pearson GD, et al: Criteria for extracorporeal membrane oxygenation in population of infants with persistent pulmonary hypertension of the newborn. *J Pediatr Surg* 1986;21:297-302.
9. Carlo WA, Chatburn RL, Martin RJ: Randomized trial of high-frequency jet ventilation vs conventional ventilation in respiratory distress syndrome. *J Pediatr* 1987;110:275-282.
10. Cornish DJ, Gerstmann DR, Clark RH, et al: Extracorporeal membrane oxygenation and high-frequency oscillatory ventilation: Potential therapeutic relationships. *Crit Care Med* 1987;15:831-834.
11. Wung JT, James S, Kilchevsky E, et al: Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 1985;76:488-494.
12. Kohelet D, Perlman M, Kirpalani H, et al: High-frequency oscillation in the rescue of infants with persistent pulmonary hypertension. *Crit Care Med* 1988;16:510-516.
13. Bohn D, Tamura M, Perrin D, et al: Ventilatory predictors of pulmonary hypoplasia in congenital diaphragmatic hernia, confirmed by morphologic assessment. *J Pediatr* 1987;111:423-431.
14. Mammel MC, Boros SJ, Coleman JM, et al: Neonatal high-frequency jet ventilation: Four years' experience. *Pediatrics* 1985;75:657-663.
15. Boynton BR, Mannino FL, Davis RF, et al: Combined high-frequency oscillatory ventilation and intermittent mandatory ventilation in critically ill neonates. *J Pediatr* 1984;105:297-302.
16. Donn SM, Nicks JJ, Bandy KP, et al: Proximal high-frequency jet ventilation of the newborn. *Pediatr Pulmonol* 1985;1:267-271.
17. Schumacher RE, Barks, JDE, Johnston MV, et al: Right-sided brain lesions in infants following extracorporeal membrane oxygenation. *Pediatrics* 1988;82:155-161.
18. Mammel MC, Gordon MJ, Connett JE, et al: Comparison of high-frequency jet ventilation and conventional mechanical ventilation in a meconium aspiration model. *J Pediatr* 1983; 103:630-634.
19. Karlson KH, Du Rant RH: High frequency positive pressure ventilation in experimental meconium aspiration syndrome. *Am J Med Sci* 1986; 29:92-96.
20. Trindade O, Goldberg RN, Bancalari E, et al: Conventional vs high-frequency jet ventilation in a piglet model of meconium aspiration: Comparison of pulmonary and hemodynamic effects. *J Pediatr* 1985;107:115-120.

In Other AMA Journals

JAMA

Does Taking Vitamins at the Time of Conception Prevent Neural Tube Defects?

L. B. Holmes (*JAMA* 1988;260:3181)

Diarrheal Deaths in American Children

M. S. Ho; R. I. Glass; P. F. Finsky; N. Young-Okoh; W. M. Sappenfield; J. W. Buehler; N. Gunter; L. J. Anderson (*JAMA* 1988;260:3281)

George Armstrong (1719-1787)

Founder of the First Dispensary for Children

Harry Bloch, MD

An intractable aspect of human behavior in every stage and structure of society has been inhumanity to children.[1-7] England's social form in the 18th century, distinguished by a swiftly accelerating industrial revolution, evidenced human violence toward children in the inordinate incidence of sickly and deformed infants, illegitimacy, an infant mortality that reached 75% before the age of 2 years, abandonment of unwanted infants, and infanticide and a mortality in London's Foundling Home so depressingly high that William Cadogan (1711-1791) proffered his treatise as a guide to better care.[7-10]

See also p 242.

English society in the 18th century included factory and mill owners dehumanized by profit and greed; the aristocracy of blood dehumanized by idleness and frivolity; and the lower classes abandoned to squalor. The cheap and obedient labor—children, women, and men—were forced to work long hours with little rest, comfort, food, or recompense. They suffered poverty, deprivation, periods of unemployment, and, in despair, addiction to cheap gin and ale, but worse was the confinement to oppressive, crowded, unhygienic slums that spawned disease and that were particularly harmful to infants in the summer months. The newly rich and the nobility were indifferent to the moral consequences of mass employment of young women in mills and factories and as domestics, the lot and fate of child workers who were victims of rapacity and savagery, and the care and well-being of infants and children of the slums who sickened and succumbed in large numbers.[11-14] Illegitimacy only began to wane in the 19th century with the availability of contraception and abortion.

The focus of this essay is an 18th century Scottish doctor practicing in London who was profoundly distressed by the lack of medical care and the high mortality of sick children in the slums of London. He felt it was his "imperative duty" to devote his life and means to these victims of poverty, and to provide them with medical care and medicines gratis. In this process, George Armstrong was swept into a life as a physician to thousands of sick children, and into unforseen and challenging components in the practice of pediatrics.

Armstrong was the son of a rural minister in Scotland. He earned an arts degree and qualified as a general practitioner in medicine without a degree at Edinburgh University with funds supplied by an older brother.[15,16] John Armstrong (1709-1779), the older brother, left for London after obtaining a degree in arts and medicine, and embarked on a successful career as a poet-physician.[15,17] He has been identified as the author of an unsigned pediatric anthology with the following preface: "Despite the teaching of Harris, physicians in the fear of doing mischief or that nothing can be done for sick children have commonly resigned those little patients to ignorant nurses and old women."[18,19] The anthology was a revision of a text by Walter Harris (1647-1732), with the addition of a preface and excerpts from various authors.[20]

George Armstrong left Scotland for London in 1744 to serve in a military hospital. He married Ann Rawlins (1737-1816) in 1755, settled in the London suburb of Hampstead, and had his earliest pediatric experiences. The birth of his first child catapulted Armstrong into a terrifying pediatric predicament. The failure of Ann's breast milk compelled feeding the newborn by the dreaded artificial, or "hand," method, of which Armstrong had no knowledge or experience. He was fully aware of its ominous risk, but with the guidance of Cadogan's essay, and with patience and prudence, the infant survived on fresh cow's milk fed by spoon or horn. The Holborn slums, where Armstrong made charity calls, were established as a guidepost in pediatrics for the rest of his life. He watched poverty ravage the health and well-being of deprived children, and saw the swiftness with which they perished in sickness.[15]

In February 1769, Armstrong took the initial step toward realizing his goal. He circulated a preliminary proposal for a dispensary to offer medical care and medicines gratis to sick infants and children of the poor.[21] In an essay (1767) and in the published final proposal (1769), he contended that medical care was not available to children of the lower classes; that hospital admission was not accessible to patients under 4 years of age; and that a dispensary was necessary.[22,23] Shortly thereafter, the dispensary materialized in London (1769).

Four mornings a week, George Armstrong set out from Hampstead by foot or coach to arrive at the dispensary before noon, a distance of four miles. Alone and unaided, he nurtured his project and no obstacle was tolerated, regardless of time, on a visit to a sick child. It was not until nightfall

Accepted for publication Oct 27, 1988.

From the Department of Pediatrics, State University of New York, NY Downstate Medical School, Kings County Hospital Medical Center, and Brookdale Hospital Medical Center, New York.

Reprint requests to 49 Crest Dr, South Orange, NJ 07070 (Dr Bloch).

that he returned to Hampstead and resumed calls on waiting patients. Realizing the need to conserve his meager resources (almost the entire expense of the dispensary was defrayed by Armstrong himself), his time and energy (when a terminally ill child, sent home to spend its last days with the family, died, he hurried back to London, heedless of fatigue, to view the autopsy), Armstrong rented larger quarters (1771), moved his family there, and saw both paying patients and sick children.

The dispensary continued to grow and develop, and Armstrong grew and developed. Adding to an innate humanism, sensitivity to the needs of sick children, judgment, and common sense, Armstrong became enriched with pediatric experience, diagnostic and observational skills, knowledge of morbid anatomy, and a scientific spirit. He gathered facts on children's diseases, morbid anatomy, therapeutics, and the nursing and management of infants, and incorporated all that he learned into a series of erudite essays that portrayed a physician who was pragmatic, skilled, and knowledgeable in the pediatrics of the time.[23]

Armstrong, proud of the dispensary, boasted: "No institution has done so much good and saved so many lives at so little expense." He advised that wet nurses should have strong nerves, be healthy, sober, clean, and of good temper, and have plenty of milk. He instructed mothers about disease prevention in infants and children, their diet, exercise, cleanliness, and clothing, and warned against feeding fats, gin, and ale. "Doctors," he stated, "have been deprived of the knowledge and experience to be found in the fund of diseases and pathology at the dispensary that would promote confidence, understanding, and help reduce mortality." This was the beginning of clinical instruction.[24]

The dispensary aroused scant interest among London's doctors. Some called it a futile and extravagant endeavor, and James Coakeley Lettsom (1744-1815) charged that (1777): "Lives are being sacrificed to experimental mass treatment."[8] The criticism was unfounded, and did not deter Armstrong from his self-appointed purpose. In December 1781, burdened with debts and a lawsuit and arrest for nonpayment of a loan, he suffered a stroke and paralysis of the left side. For the remainder of his life he lived in want, unrewarded and in obscurity; when he died, it passed unnoticed in the *London Medical Journal*, but not in the memories of 35 000 children.[15]

George Armstrong's essays constitute a chronicle of the dispensary, the early development of the science of pediatrics, and the concurrent growth and development of their author. At the request of the publisher, he painfully made the last revision (1783); a final edition, after his death, was edited by A. P. Buchan in 1803.[23] In this collection, Armstrong defined all the diseases of children that he experienced, compared clinical and postmortem findings, and recorded the effectiveness of remedies given at the earliest observed changes in symptoms and signs. To evaluate the effectiveness of medications, he made original therapeutic experiments: patients with the same disease were divided into large groups; each was tested with a different remedy and results were compared.

Armstrong used the common remedies of the time (blood letting with lancet and leech, blisters, pukes), but he always sought better means of treatment. In "hopping cough," a few drops of antimonial solution given two or three times daily proved expedient and caused few deaths; the tincture of the bark of cantharides or the extract of hemlock were equally effective.

The protean manifestations, course, and postmortem findings in tuberculosis became familiar to Armstrong, and he always tried to relate clinical and postmortem evidence to further tuberculosis' therapeutics. He was aware of the hopelessness of therapy, especially when he viewed at autopsy the adhesions of abdominal viscera. Nonetheless, Armstrong hopefully treated city children with rest and sea air, and those from coastal regions with a dry inland climate. He was deeply affected by the many failures.

The symptoms of diarrhea, constipation, anorexia, and vomiting were considered by Armstrong to be serious evidence of intestinal toxemia, and were particularly ominous in infants fed by hand. He discovered that the earliest clue, twitchings of the muscles of the face and eyes, demanded immediate cleansing of the intestine; if not instituted promptly, vomiting, green watery stools, convulsions, and death ensued. He named this phenomenon "inward fits" (reflex neuromuscular irritability was still unknown). Subsequently, Armstrong wrote that twitchings are normal in infants up to 3 months of age, but starting caused by noise or the sudden approach of a person can be suggestive of polio.

Armstrong described the postmortem appearance of pyloric stenosis, and was incorrectly credited with the first report of a case.[25] He was not aware of the earlier account by Patrick Blair.[26] Armstrong's description did, however, antedate that of Hezikiah Beardsley (1748-1790), reported in 1788. In the same essay (1771), he advised gentle massage of newborns and infants, and hydrocephalus internus was clearly depicted.

Armstrong's writings were, in great part, plagiarized by Michael Underwood (1787-1820),[27] who was accused by a French physician of "stealing" from George Armstrong.[28] Underwood believed in the perils of teething, but Cadogan and Armstrong were among the few who rejected the claim of its dangers and mortality. Accused by Underwood as an enemy of breast-feeding, Armstrong replied: "I am no advocate of bringing up infants by hand feeding; and I do not advise dry nursing of infants."

It was not until the 20th century that Armstrong, his dispensary, and his essays came out of "the suit of night."[15-17,21] The dispensary has been descibed as the most important step ever taken in England toward the care of sick children.[24] He is praised as an early activist,[29] founder of the first hospital for children,[30] and patron saint of preventive medicine with practical and sound therapeutics.[8,31] He is esteemed as:

> The organizer of the first hospital for children, pioneer physician-philanthropist with a true scientific spirit and a prophetic outlook who made therapeutic experiments, compared clinical and post-mortem appearances and died in obscurity, un-

praised, and unrewarded except in the grateful remembrance of the poor in London.[25]

He is extolled as a noble benefactor in the cause of infancy, the originator of the dispensary movement, and a medical pioneer of social welfare for children; it has been stated that before the days of Armstrong, infants of the lower classes received little or no attention in times of sickness.[7] It is of interest that in the 50-year index (1933-1982) of the *Bulletin of the History of Medicine*, there is not a single mention of him.

In summary, the intractable aspect of human behavior in every stage and structure of society has been violence to children. This was exemplified in England at the beginning of its Industrial Revolution in the 18th century. In response to experiences with infants and children in London's slums, Armstrong, alone and unaided, created the first dispensary for the free medical care of infants and children. His venture survived a little more than a dozen years, and the founder, the dispensary, and his essays were forgotten for two centuries.

References

1. Paine GH: *The Child in Human Progress.* New York, Putnam, 1936.
2. Riches D (ed): *The Anthropology of Violence.* New York, Basil Blackwell, 1979.
3. Beck J: *Infanticide.* New York, Seymore, 1817.
4. Mosely KI: The history of infanticide in Western society. *Issues Law Med* 1986;1:345.
5. Rotten E: *Children, Wars, Victims.* Paris, UNESCO, 1949.
6. Lifton RG: *The Nazi Doctors.* New York, Basic Books Inc Publishers, 1986.
7. Maruki I, Maruki T: *The Hiroshima Panels.* Tokyo, Nyi Shobo, 1959.
8. Caulfield E: *The Infant Welfare Movement in the 18th Century.* New York, Hoeber, 1931.
9. Ruhräh J: *Pediatrics of the Past.* New York, Hoeber, 1925
10. Cadogan W: *An Essay Upon Nursing and the Management of Children.* London, Horsfield, 1750.
11. Jackson TH: *Charles Dickens.* New York, International Press, 1981.
12. Engels F: *The Condition of the Working Class in England.* London, 1892.
13. Belmer GK: Deadly motherhood, Mid-Victorian England. *J Hist Med Allied Sci* 1979;34:403.
14. Forbes TR: Deadly Parents: Child homicide in 18th and 19th century England. *J Hist Med Allied Sci* 1986;4:175.
15. Maloney WJ: *George and John Armstrong of Castleton.* Edinburgh, E & S Livingstone, 1954.
16. Maloney WJ: John and George Armstrong in Edinburgh. *Edinburgh Med J* 1950;57:600.
17. Maloney WJ: John and George Armstrong in London. *Edinburgh Med J,* 1951, vol 58.
18. Caulfield E: A full view of all the diseases incident to children. *Ann Med Hist* 1928;10:409.
19. Armstrong J: *A Full View of All Diseases Incident to Children.* London, Millar, 1742.
20. Harris W: *De Morbis Acutis Infantum.* London, Smith, 1689.
21. Poynter FNL: A unique copy of George Armstrong's proposal for establishing the Dispensary for Sick Children, London 1769. *Med Hist* 1957;1:65.
22. Armstrong G: *A General Account of the Dispensary for the Relief of the Infant Poor.* London, Cadell, 1769.
23. Armstrong G: *An Essay on Diseases Most Fatal to Infants, to Which Is Added Rules to Be Observed in the Nursing of Children; With a Particular View to Those Who Are Brought up by Hand.* London, Cadell, 1803.
24. Still GF: *The History of Pediatrics.* Oxford, England, Oxford University Press, 1931.
25. Foote JA: Pylorospasm. *AJDC* 1918;15: 351.
26. Blair P: An account of the dissection of a child. *Philosoph Trans Soc* 1717;853:631.
27. Underwood M: *Treatise on the Diseases of Children With the Directions of the Management of Infants From Birth.* London, Mathews, 1789.
28. DeVillebrune JBI: *Traité des Maladies des Infants.* Paris, Barrois, 1786.
29. Charney E: George Armstrong: An early activist. *AJDC* 1974;128:826.
30. Abt-Garrison: *History of Pediatrics by Various Authors.* Philadelphia, WB Saunders Co, 1965.
31. Ruhräh J: George Armstrong. *AJDC* 1930;40:1094-1098.

In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY

The Large Vestibular Aqueduct Syndrome in Children: A Review of 12 Cases and the Description of a New Clinical Entity

Mark J. Levenson, MD; Simon C. Parisier, MD; Morton Jacobs, MD; David R. Edelstein, MD (*Arch Otolaryngol Head Neck Surg* 1989;115:54-58)

Nasal Symptoms Associated With Abuse During Adolescence

Richard H. Schwartz, MD; Todd Estroff, MD; David N. F. Fairbanks, MD; Norman G. Hoffmann, PhD (*Arch Otolaryngol Head Neck Surg* 1989;115:63-64)

The *AJDC* Archives

November 1930
(*AJDC* 1930;40:1094-1098)

Pediatric Biographies
George Armstrong

John Ruhräh, MD
Baltimore

George Armstrong, one of the most notable figures in the history of pediatrics, was the brother of the physician-poet, John Armstrong, and like him was endowed with a peculiar personality which militated against his chances of continued success. Little is known about him, not even the date or place of birth. Caulfield stated that his father was Robert Armstrong, a minister of Castleton, 1693-1733, which would bring

See also p 239.

the date of his birth sometime before 1735. He practiced pharmacy at Hempstead, and then, after qualifying as a physician, went to London and started the first hospital and dispensary for the children of the poor in a house in Red Lion Square. Infants up to 4 years of age were treated, as half of those born in London died by that time. This establishment was opened in 1769 and was in operation until 1781, when, according to Buchan, it was closed for lack of financial support. Armstrong gives a different reason (Caulfield):

> But as that charity has been at a stand for some time on account of my bad state of health which put it out of my power to attend it (he was stricken with a "paralytic complaint" about this time) I shall not trouble the Public with a particular detail of the Institution, contenting myself with explaining the nature and usefulness of it, which, perhaps, may some time or other induce some other person to take it up.

The date of Armstrong's death is usually given as 1781 (Boas, Index Catalogue), but Caulfield called attention to the fact that he was evidently alive after the closing of the dispensary in this year.

Armstrong made good use of the immense clinical and pathologic material at his disposal, and the little book which he had issued in 1767 with the title of "An Essay on the Diseases Most Fatal to Infants, to Which Are Added Rules to be Observed in the Nursing of Children, with a Particular View to Those Who Are Brought Up by Hand," was translated into German the same year by George Conrad Gsellius; another German translation dated Regensburg, 1786, is by D. Jac. Christian Gottl. Schäffer, and an Italian edition by some one unknown was published in 1793. It was reprinted with additions in 1771, and in 1777, a second volume was issued entitled: "An Account of the Diseases Most Incident to Children from Their Birth to the Age of Puberty."

With this was also the pamphlet "A General Account of the Dispensary for the Infant Poor" which had been issued separately in 1769 as propaganda for raising funds for the dispensary. This was reprinted in 1783, and in 1808, A. P. Buchan reedited it with additions and included the essay on nursing which had been printed in shorter form in 1772.

In that most interesting book, "Medical Bibliography A.B.," James Atkinson of York comments on Armstrong as follows:

> There is considerable practical information, and much childishnous about Armstrong. He recommends his profession with warmth, and laments its neglect and abuse

AN

ESSAY

ON THE

DISEASES

Moft Fatal to INFANTS.

To which are added

RULES to be obferved in the NURSING of Children:

With a particular View to thofe who are brought up by HAND.

LONDON
Printed for T. CADELL, in the Strand.
MDCCLXVII.

Title page.

with censure. The cradle and the nursery have been much obliged to him; for he who saves the king's subjects, earns him a great deal of money; and he who preserves the life of a child, rescues it at least from a very stupid sojourn in limbo.

Armstrong visualized the possibilities of infant welfare, especially that part dealing with the treatment of the sick child. He put some of his ideas into practice, but something, just what is a question, prevented his institution from enjoying a lasting success, and he died in obscurity and poverty, the fate of most of those who seek to help their fellow men without thought of their own old age.

He was not a bad physician, for while he was given to "antimonial pukes" and sometimes bled and blistered, his therapeutics were reasonably sound, especially so for the age in which he lived. He knew the danger of opium and the virtues of rhubarb, calomel and mercury and chalk. He also knew the value of proper diet and the care of the child.

His book includes among other things accounts of inward fits, watery gripes, convulsions and thrush. In the 1771 edition of his book he describes three cases of pyloric stenosis, so far the first noted in the earlier literature. This is in his account of watery gripes and is as follows:

In a child about three weeks old, that died of watery-gripes some time since, and which I opened, I found most of the stomach, towards the upper orifice, and almost the whole fundus, in the same tender state with that of the child just now mentioned. But towards the *pylorus, the* structure was firm enough, as likewise that of the intestines, both small and great. The stomach was quite distended with curdled milk and victuals, with which the nurse had crammed the child, mixed likewise with some of the chalk julep, but the whole intestines were remarkably empty. There was no morbid appearances to be observed any where but in the stomach; and this *viscus* being so full, while the intestines were almost empty, it looked as if the disease had been chiefly owing to a spasm in the *pylorus,* which prevented the contents of the stomach from passing into the *duodenum.* Perhaps, cases of this kind are more frequent than is commonly imagined; and it might probably be owing to the tender state of the stomach, that the antimonial solution, which was given the child, had but very little effect; and I have commonly observed, that when vomiting or purging medicines, given to infants in a sufficient quantity, have not the usual effect, it is a very bad sign. What is remarkable, this was the third child (and they have never had any more) which the parents have lost at the same age, and in the same disease.

His ideas on infant feeding are interesting, especially his description of the horn for feeding which he thinks superior to the feeding boat or spoon. Note also his use of massage or friction.

But though, as I just now observed, I do not advise dry-nursing of infants, when they can be properly suckled, yet I would not have parents to be discouraged from trying it when it becomes requisite, being firmly persuaded, that if a child is born pretty strong and healthy, it had better be brought up by hand, in the method to be afterwards explained, than suckled by an ailing nurse, or one that has not a sufficient quantity of milk. For, when I talk of a child's being properly suckled, I mean by a nurse who is healthy, sober, good-tempered, cleanly, careful, and has plenty of good milk. A wet-nurse ought likewise to have pretty strong nerves; for if they are weak, the least surprise has a bad effect upon the milk; or if the child happens to be suddenly taken ill, from the fright and anxiety, the milk is sometimes quickly dried up, when, perhaps, the poor infant has the most occasion for it. For this reason, some mothers, who are very fond of their children, make but bad wet-nurses, though well enough qualified for it in other respects.

There are two ways of feeding children who are bred up by hand; the one is by means of a horn, and the other is with a boat or spoon. They both have their advocates; but the latter, in my humble opinion, is preferable.

The horn made use of for suckling, is a small polished cow's horn, which will hold about a gill and a half. The small end of it is perforated, and has a notch round it, to which are fastened two small bits of parchment, shaped like the tip of the finger of a glove, and sewed together in such a manner, as that the food poured into the horn can be sucked through between the stitches. This appears to be a very simple and ingenious contrivance, and is admired by some, who look upon it as a kind of artificial nipple; and it might very well be considered as such, if we had but the breast-milk to convey through it. Or if we could discover any food of the same thinness with the milk, and as nourishing as it is, the horn might still answer. But as a discovery of this kind is not to be expected, and the food which the child sucks through this artificial nipple must be thin, in order to pass between the stitches, there requires a larger quantity of it to nourish the child, and hence its stomach and bowels are too much relaxed, whereby it is in danger of falling into the watery gripes, as was the case with two of mine, which were fed for some time in that way.

While the child is suckled, I think the best food is crumb of bread boiled in soft water, to the consistence of what is commonly called pap, or a thin panado. The bread should not be new baked, and, in general, I think roll is preferable to loaf bread.

This pap should be sweetened with soft or Lisbon sugar, unless the child is of a lax habit of body, in which case the finest loaf sugar should be used; and in this case too, the pap should be made with biscuit instead of roll. It should not be made sweeter than new milk; for too much sugar both palls the appetite, and grows sour upon their stomachs.

Before the child is weaned, the victuals should be made thicker, by which means it will become less fond of the breast, and consequently, as was mentioned above, easier to wean.

If the infant is to be bred up by hand from the birth, it ought to have new cow's milk mixed with its victuals as often as possible, and now and then some of it alone to drink. Asses' milk will be still better, when it can be conveniently had, and the parents can afford it.

But the most useful exercise for very young infants, is rubbing with the hand; which cannot be too often repeated, nor continued too long at a time. They should be well rubbed all over, before the fire, twice a day at least, that is, morning and evening, when they are dressed and undressed; and the rubbing should be repeated from the loins downwards, every time they are turned dry, unless they have a purging, when it might fatigue them to have it done so often. There is nothing that infants in general seem more delighted with than this exercise, and it were to be wished, that the nurses

would indulge them more in it. It will frequently make them quiet when nothing else will, and it is not only very pleasing to them, but conduces greatly to make them thrive, and to prevent their catching cold, by promoting a free circulation, and perspiration likewise; Providence having kindly connected the agreeable sensation and the benefit.

They are particularly fond of cramming them with fat, from a mistaken notion, that it must be light of digestion, because it weighs light in the scale; whereas, on the contrary, to most stomachs, there are few things so hard to be digested as fat.

Many poor children are likewise hurt by being crowded together in small close apartments, which is not so easily remedied; but in this case I always advise them to keep the windows open in the day-time, while the weather is hot, and the doors of the bed-chambers and closets during the night. I also object strongly to their living in stable-yards, the air of which is particularly unwholesome to children, as was before mentioned.

Armstrong's Dispensary was an interesting place, and it has been estimated that about 35,000 children were treated there. His reasons for establishing it are given in "A General Account of the Dispensary for the Relief of the Infant Poor," in which among other things he states:

It was likewise observed, that Children, till they arrive at three or four Years of Age, cannot be received into Hospitals (except in Cases of Accidents and the Stone) for several obvious Reasons; and though they might be admitted as Out-Patients, yet as none of the Hospital-Physicians see their Out-Patients oftner than once or twice a Week, and as the Complaints of Children, especially during the tender State of Infancy, frequently require more immediate Relief; if there was a Place established for giving Advice and Medicines several Times in the Week to the Children of the Poor, by a Person, who, from his Success in treating the Diseases of Infants for some Years past, hoped he might be deemed qualified for such an Undertaking, the great Mortality of Children might be diminished in some considerable Degree; as it could not be denied that Numbers were lost for want of timely Assistance.

For this Purpose a House was taken in *Red Lion Square*, where Attendance was given four Days in a Week, *viz. Mondays, Wednesdays, Fridays* and *Saturdays*, from Twelve till Two, to administer Adice and Medicines *gratis* to poor Children; and this Charity has been continued ever since, under the Denomination of, *The Dispensary for the Infant-Poor.*

But as it was not reasonable to expect, that the Institutor of this Charity should, besides his Time, Attendance, and Labour, bear all the Expenses of it; such as paying for the House, Medicines, and proper Assistance; it was proposed, that these Expenses should be defrayed in the following Manner: "That every Person subscribing One Guinea *per Annum*, should be intitled to have always one Patient at a Time on the Dispensary-Books; and every Person subscribing Two Guineas, to have two Patients; and so on, in the like Proportion."

Commentary

Historical perspectives are important to any discipline; in pediatrics, learning of our antecedents often teaches us much about our current ethos. Our customs, habits, interests, and behavior are often conditioned by what went before, although we may be unaware of the historic train that brought us to the present. *AJDC* believes that it is useful to remind ourselves periodically of our past, and of the evolutionary steps our forebearers made in the development of our profession.

In 1930, Dr Ruhräh summarized the life and times of George Armstrong. Dr Bloch, in this issue of *AJDC*, gives us a modern reminder of this pioneering Scottish physician. Armstrong's "imperative duty" is reminiscent of many pediatricians' attitudes and behavior today. He saw evil in the way children were treated and in the ravages of poverty and attendant disease, and took steps, brave ones in his day, to assist these children in their plight. He resisted the scorn and impatience of his colleagues, and plowed forward with his dispensary and his untiring personal efforts. How like the many pediatricians today, who, in the face of society's indifference, fight for legislation and regulation to better childhood life and limb. These men and women also give unstintingly of their time and effort, often with little or no compensation save for their satisfaction in doing what they believe to be right and just.

Armstrong also attempted to communicate his ideas and experience to others by means of his essays, forerunners of the medical literature of which *AJDC* is proud to be a distant relative. That tradition of physicians communicating their ideas to their peers and colleagues persists in a form and extent that would amaze Armstrong, were he to return today. We note with rue and amusement that even he was plagiarized in those days, echoing a tradition that unfortunately persists to a small extent.

Thus, the lessons that this single physician teaches us are those that thousands of individuals in our profession practice: continuing a rich humanitarian trend, with its associated desire to spread the word to others, so that many more children can benefit from one person's ideas, experience, and wisdom. We at *AJDC* are very proud to be a part of that tradition, and to be able to remind our readers of it through essays such as those of Drs Ruhräh and Bloch.

VINCENT A. FULGINITI, MD
Editor, *AJDC*
PO Box 43700
Tucson, AZ 85733

98% of subjects tested preferred EryPed*

Kristen thinks EryPed 200

"Tastes like strawberry."

**How do you turn defiance into compliance?
Specify the erythromycin kids really like... EryPed.**

- Available in delicious mixed-fruit or banana flavor
- Contains no dyes, artificial colors, or preservatives
- Requires no refrigeration
- Offers dosage flexibility—b.i.d., t.i.d., or q.i.d.†
- Can be taken with or without meals

*Data on file, Abbott Laboratories. Flavor evaluations conducted with 20 adult volunteers. Evaluations compared EryPed 200 and 400 to Barre's formulation of erythromycin ethylsuccinate oral suspension, USP 200 mg base/5 ml and 400 mg base/5 ml, respectively.

†q12h, q8h, or q6h.

Write

There's no substitute for compliance

EryPed® 200, 400 or Drops

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Please see accompanying brief summary of prescribing information.

8113876

THE EXPANDED **EryPed**® LINE, FROM ABBOTT

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Brief Summary of Prescribing Information

DESCRIPTION: Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration.

EryPed 200 and EryPed Drops (erythromycin ethylsuccinate for oral suspension) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 ml (teaspoonful) or 100 mg per 2.5 ml (dropperful) with an appealing fruit flavor. EryPed 400 when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 ml (teaspoonful) with an appealing banana flavor. After mixing, EryPed must be stored below 77°F (25°C) and used within 35 days; refrigeration is not required. These products are intended primarily for pediatric use but can also be used in adults.

Inactive Ingredients EryPed 200, EryPed 400 and EryPed Drops: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum, artificial flavors and other ingredients.

INDICATIONS: *Streptococcus pyogenes* (Group A beta hemolytic streptococcus): Upper and lower respiratory tract, skin, and soft tissue infections of mild to moderate severity.

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

When oral medication is given, the importance of strict adherence by the patient to the prescribed dosage regimen must be stressed. A therapeutic dose should be administered for at least 10 days.

Alpha-hemolytic streptococci (viridans group): Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been suggested by the American Heart Association and American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients hypersensitive to penicillin who have congenital heart disease, or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.[1] Erythromycin is not suitable prior to genitourinary or gastrointestinal tract surgery. NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]

Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

Streptococcus pneumoniae (Diplococcus pneumoniae): Upper respiratory tract infections (e.g., otitis media, pharyngitis) and lower respiratory tract infections (e.g., pneumonia) of mild to moderate degree.

Mycoplasma pneumoniae (Eaton agent, PPLO): For respiratory infections due to this organism.

Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity when used concomitantly with adequate doses of sulfonamides. (See sulfonamide labeling for appropriate prescribing information). The concomitant use of the sulfonamides is necessary since not all strains of *Hemophilus influenzae* are susceptible to erythromycin at the concentrations of the antibiotic achieved with usual therapeutic doses.

Chlamydia trachomatis: For the treatment of urethritis in adult males due to *Chlamydia trachomatis*.

Ureaplasma urealyticum: For the treatment of urethritis in adult males due to *Ureaplasma urealyticum*.

Treponema pallidum: Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae: As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

Corynebacterium minutissimum: For the treatment of erythrasma.

Entamoeba histolytica: In the treatment of intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes: Infections due to this organism.

Bordetella pertussis: Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Legionnaires' Disease: Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

CONTRAINDICATIONS: Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS: Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. There have been reports of hepatic dysfunction, with or without jaundice occurring in patients receiving oral erythromycin products.

Areas of localized infection may require surgical drainage in addition to antibiotic therapy.

Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Usage during pregnancy and lactation: The safety of erythromycin for use during pregnancy has not been established.

Erythromycin crosses the placental barrier. Erythromycin also appears in breast milk.

ADVERSE REACTIONS: The most frequent side effects of erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

HOW SUPPLIED: EryPed 200 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 ml (**NDC** 0074-6302-13), 200 ml (**NDC** 0074-6302-53), and 5 ml unit dose in ABBO-PAC® packages (**NDC** 0074-6302-05). Each 5 ml (teaspoonful) of reconstituted suspension contains activity equivalent to 200 mg erythromycin.

EryPed 400 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 60 ml (**NDC** 0074-6305-60), 100 ml (**NDC** 0074-6305-13), 200 ml (**NDC** 0074-6305-53), and 5 ml unit dose in ABBO-PAC packages (**NDC** 0074-6305-05). Each 5 ml (teaspoonful) of reconstituted suspension contains activity equivalent to 400 mg erythromycin.

EryPed Drops (erythromycin ethylsuccinate for oral suspension) is supplied in 50 ml bottles (**NDC** 0074-6303-50). Each 2.5 ml dropperful (1/2 teaspoonful) of reconstituted suspension contains activity equivalent to 100 mg of erythromycin.

After reconstitution, EryPed must be stored below 77°F (25°C) and used within 35 days; refrigeration not required.

REFERENCE: 1. American Heart Association. 1977. Prevention of bacterial endocarditis. Circulation 56: 139A-143A. 8113876

Abbott Laboratories
North Chicago, IL60064

STREP TEST™
SHEEP BLOOD AGAR PLATES
LABORATORY CULTURE MATERIALS

- BACITRACIN DISKS
- URI-DIP®
  URINE CULTURE MATERIALS
- DELUXE INCUBATORS
- DISPENSERS
- INNOCULATING LOOPS
- SWABS

AVAILABLE FROM:

UNIVERSAL BIOLOGICAL LABS
DIAGNOSTIC DIVISION OF:
NATIONAL BIOLOGICAL CORPORATION

1532 ENTERPRISE PARKWAY
TWINSBURG, OHIO 44087
(216) 425-8180
OUTSIDE OHIO: 1-800-338-5045
IN OHIO: 1-800-227-6294

ORDER TODAY
FOR IMMEDIATE DELIVERY

You're never too old to quit blowing smoke.

No matter how long or how much you've smoked, it's not too late to stop. Because the sooner you put down your last cigarette, the sooner your body will begin to return to its normal, healthy state.

American Heart Association
WE'RE FIGHTING FOR YOUR LIFE

Don't Forget!

Send for the latest edition of the free Consumer Information Catalog. ☐ The Catalog lists over 200 selected federal publications of consumer interest on subjects like health, nutrition, federal benefits, money management. ☐ The Catalog is free and so are many of the booklets. ☐ Just send your name and address, no strings attached. Write today:

Consumer Information Center
Department DF
Pueblo, Colorado 81009

Consumer Information Catalog

U.S. General Services Administration

Re-introduce The Oldest Advance In Medicines.

It's called talking. If your older patients don't ask you about the prescriptions they've been given, make it a point to tell them what they need to know. Make sure they know the medicine's name, how and when to take it, precautions, and possible side effects. Encourage them to write down the information and ask you questions about things they don't understand.

You'll also want to take a complete medications history including both prescription *and* non-prescription medicines. The history can alert you to the potential for drug interactions and help you simplify their regimen.

Re-introduce the oldest advance in medicines. Make talking a crucial part of your practice. Because good, clear communication about medicines isn't a thing of the past. It's the way to a healthier future.

Before they take it, talk about it.

National Council on
Patient Information and Education.
666 Eleventh St. N.W. Suite 810
Washington, D.C. 20001

Now, MDI therapy is available to more patients than ever before

New AeroChamber®
WITH *MASK* (aerosol holding chamber)

Permits easier metered-dose-inhaler (MDI) therapy in children and the elderly (see boxed statement below). The device consists of an aerosol holding chamber with a soft, flexible mask that covers the patient's nose and mouth. A one-way valve holds the medication until the patient inhales. Expired air is vented through exhalation ports. AeroChamber with *Mask* is economical and fits virtually any inhaler.

IMPORTANT INFORMATION
Package insert dosing instructions should be consulted for all metered dose inhalers (MDIs) when used with AeroChamber with *Mask*.

Dosage and administration recommendations vary for different MDIs, and the limitations and conditions of use for each product should be considered before utilizing this device, particularly for younger and older patients.

☐ **Yes, I am interested in the New AeroChamber® with *Mask*. Please send more information.** AJDC 2

☐ **Enclosed is my check or money order for:**

#Units		Price		Total
_____	×	**$22.00**	=	_____

Minimum order—6 units. Price includes postage and handling.

Name _____
(please print)
Address _____
City _____
State _____ Zip _____
Phone ( ) _____

Clip and mail to: **AeroChamber® with *Mask***
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

For more information or to place an order now, call 1-800-325-1605.

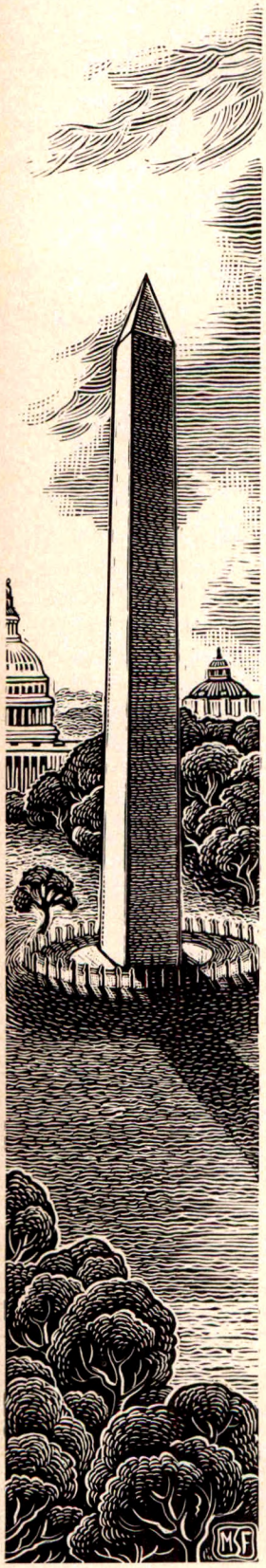
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

© 1988 Forest Pharmaceuticals, Inc.

AWM-008-88

OVER A CENTURY AGO,

a thousand visionary physicians across the nation bestowed a commemorative stone carving to the Washington Monument. This patriotic display symbolized their unrelenting devotion to a new republic founded on freedoms—including the freedom to practice medicine for the best possible health of all its people. *Today your help is needed to restore this symbol of our profession.*



Because the commemorative stone has suffered from severe erosion and defacement, the American Medical Association is launching a campaign to raise money from physicians to restore this symbol of medicine for the National Park Service. Every contribution made to this effort will serve as a statement of each physician's personal affirmation and commitment to health and medicine in America.

Please take part in rededicating the commemorative stone as a shining example of the strength of medicine in a free and strong society. Contributors who donate $100 or more will receive a memorial replica of the carving as a token of appreciation. Send your tax deductible contribution for this timeless symbol today. Thank you.

Yes, I want to affirm my commitment to health and medicine in America. Please accept my contribution for:

_____ Other
_____ $100
_____ $50
_____ $25

Please make checks payable to: AMA Stone/National Park Service. Mail your payment with this form to:

AMA Stone/National Park Service
P.O. Box 109016
Chicago, Illinois 60610-9016

Name _____

Address _____

City/State/Zip _____

All donations are tax deductible. All contributions will be publicly recognized in an unveiling ceremony for the new stone when it is fully restored.

Thank you for your contribution.

ADVERTISEMENT

THE VINDICATION OF LACTOSE

Decreased lactase levels are not as common as once believed: lactose actually helps resolve diarrhea often attributed to formula intolerance

Background

Though it is still common practice for physicians to recommend a lactose-free formula for infants with chronic nonspecific or postinfectious diarrhea, studies demonstrate that lactose is rarely the offending agent. In fact, recent clinical evidence shows that formula containing lactose may actually be helpful in resolving diarrhea.

Lactose routinely excluded from soy-based formula without intrinsic cause

Acute gastroenteritis in infants is often followed by chronic diarrhea. Conventional treatment for this involves delaying the reintroduction of usual feedings, and often withholding cow's milk or milk-based formula. Soy-based formulas are often substituted to eliminate the suspect protein. These formulas also replace lactose with sucrose and/or corn syrup for the carbohydrate source; this once seemed a good idea because congenital lactase deficiency, now regarded as extremely rare,[1] was formerly thought to be common in infants.

Protein, not lactose, is agent in most formula intolerance: guilt by association?

Most cases of lactose intolerance are temporary, secondary to protein-induced gastroenteritis, and quickly resolve as soon as the offending protein is withdrawn.[2] Liu et al[3] demonstrated convincingly that most infants initially intolerant of both milk and lactose could tolerate lactose after milk protein was eliminated from the diet. Lactose seems to play a role in formula intolerance only when associated with an offending protein. Gerrard[2] found that infants with confirmed allergy to cow's milk protein showed no signs of lactose intolerance when returned to breast milk. Also, clinical experience suggests that human milk frequently is well tolerated when other foods are not,[4,5] even though the carbohydrate of breast milk is entirely lactose. Groothuis et al[6] found that lactose formula did not prolong mild gastroenteritis in infants, but that these infants recovered as quickly as those fed formulas containing sucrose or maltodextrin.

Lactose helps resolve diarrhea

The most recent data indicate that lactose may actually resolve some of the symptoms formerly attributed to lactose intolerance or protein intolerance.[7] Forty infants were chosen who, following an initial presentation of acute gastroenteritis, were diagnosed as having chronic diarrhea and, presumably, formula intolerance. The infants were divided into three groups and fed formulas that were identical except for the carbohydrate source. Within four days, improvement was observed in 86% of the infants fed the formula containing lactose, compared with only 20% and 19% of those fed maltodextrin- or sucrose-containing formulas.

Lactose vindicated

Lactose is the carbohydrate of breast milk, the ideal infant nutritional source, and aids in the absorption of calcium,[8] magnesium, and zinc.[9] It causes beneficial biochemical and microbiological changes in the lower parts of the intestine,[10] helps establish favorable colonic flora,[11] and its galactose portion may be important in the rapid formation of brain lipids.[12] As described above, lactose may also take part in a specific mechanism for the inhibition of water and electrolyte losses through the bowel.[7] This beneficial energy source should not be eliminated from infant formulas because of outdated misinformation. The American Academy of Pediatrics Committee on Nutrition clearly states that "The current data do not suggest that lactose be routinely eliminated from the diet of infants recovering from diarrhea."[8] While the apparent hypoallergenicity of soy-based formulas may seem to make them suitable for infants with a family history of atopy, they contain no lactose; a more desirable alternative is the lactose-containing GOOD START H.A.™ Iron Fortified Hypoallergenic Infant Formula recently developed by Carnation Nutritional Products. For a product monograph write Carnation Nutritional Products, ACS, 4144 Howard Ave, Kensington, MD 20895.

REFERENCES:

1. Williams CA: Metabolism of lactose and galactose in man. *Prog Biochem Pharmacol* 1986;21:219-247.

2. Gerrard JW: Cow's milk and breast milk, in Brostoff J, Challacombe SJ (eds): *Food Allergy and Intolerance.* Eastbourne, England, Ballière Tindall, 1987, pp 344-355.

3. Liu H-Y, Tsao MU, Moore BA, et al: Bovine milk protein-induced intestinal malabsorption of lactose and fat in infants. *Gastroenterology* 1967;54:27-33.

4. Klish WJ, cited by Committee on Nutrition, American Academy of Pediatrics: *Pediatric Nutrition Handbook*, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, p 277.

5. Finberg L, Harper PA, Harrison HE, et al: cited by Committee on Nutrition, American Academy of Pediatrics: *Pediatric Nutrition Handbook*, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, p 277.

6. Groothuis JR, Berman S, Chapman J: Effect of carbohydrate ingested on outcome in infants with mild gastroenteritis. *J Pediatr* 1986;108:903-906.

7. Donovan GK, Torres-Pinedo R: Chronic diarrhea and soy formulas: Inhibition of diarrhea by lactose. *Am J Dis Child* 1987;141:1069-1071.

8. Committee on Nutrition, American Academy of Pediatrics: *Pediatric Nutrition Handbook*, ed 2, Forbes GB, Woodruff CW (eds). Elk Grove Village, Ill, American Academy of Pediatrics, 1985, pp 116, 278.

9. Zeigler EE, Fomon SJ: Lactose enhances mineral absorption in infancy. *J Pediatr Gastroenterol Nutr* 1983;2(2):288-294.

10. Grüttner R: Qualitative aspects of carbohydrates in the nutrition of infants. *Monatsschr Kinderheilkd* 1974;122(suppl 5): 264-267.

11. Braun OH: The protective effect of human milk against infections and its potential causes. *Klin Padiatr* 1976;188(4):297-310.

12. Brady RO: Sphingolipidoses and other lipid metabolic disorders, in *Basic Neurochemistry*, ed 3. Boston, Little Brown & Co, 1981, pp 615-624.

© 1988 Carnation Nutritional Products Printed in USA NP-010 9/88

Carnation®

Cough and cold therapy as individual as your patients' symptoms.

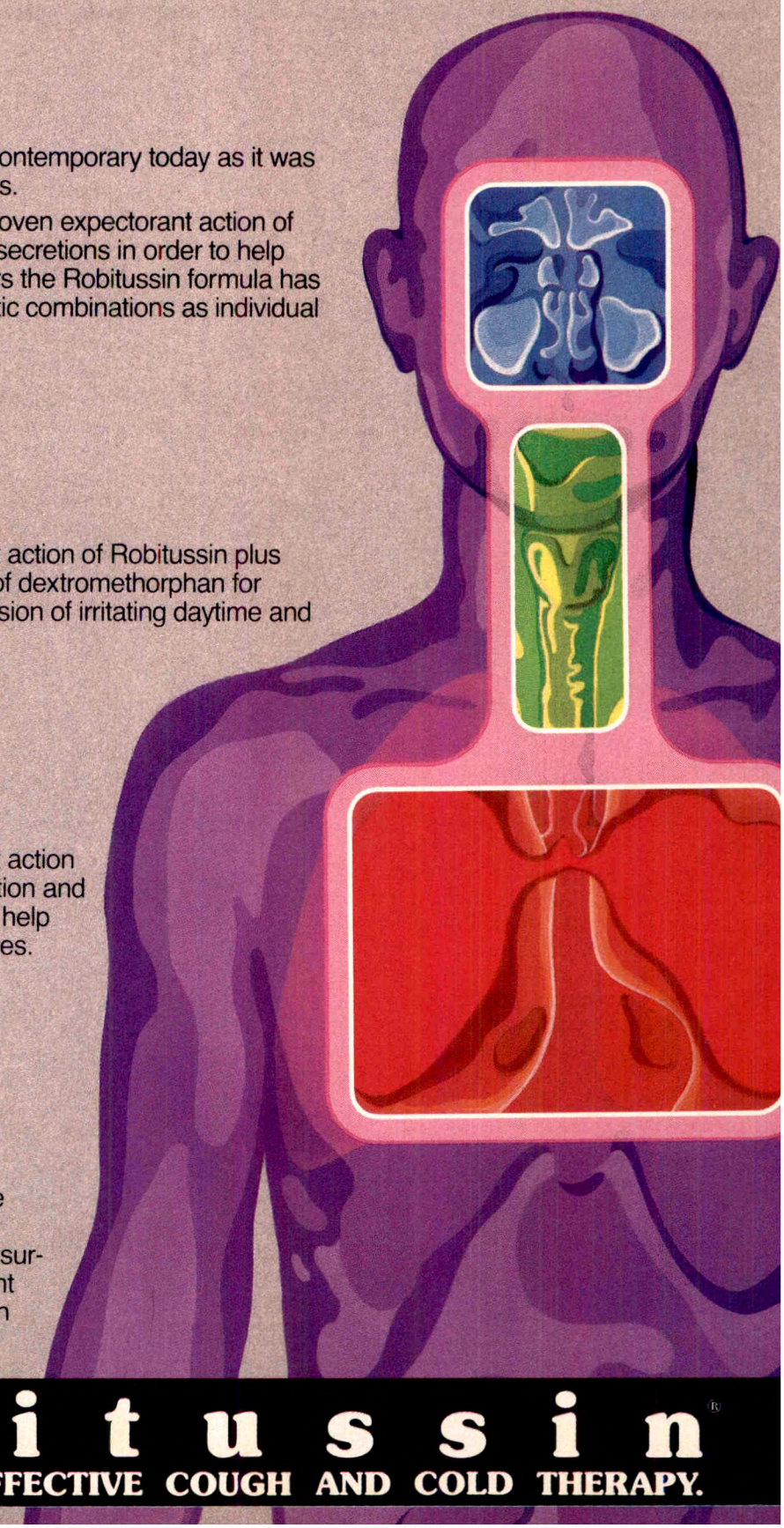
Robitussin® is as contemporary today as it was 40 years ago because efficacy is timeless.

Every Robitussin formula contains the proven expectorant action of guaifenesin to thin and loosen bronchial secretions in order to help clear chest congestion. Through the years the Robitussin formula has been expanded to form special therapeutic combinations as individual as your patients' symptoms.

Robitussin® DM® provides the expectorant action of Robitussin plus the unsurpassed, non-narcotic efficacy of dextromethorphan for effective, centrally acting cough suppression of irritating daytime and nighttime coughs.

Robitussin® PE® provides the expectorant action of Robitussin to help clear chest congestion and adds an effective nasal decongestant to help clear congested nasal and sinus passages.

Robitussin® CF® provides more complete cough and cold relief by combining the expectorant action of Robitussin, the unsurpassed, non-narcotic cough suppressant activity of dextromethorphan and proven nasal congestion relief.



Robitussin®

A TRADITION OF EFFECTIVE COUGH AND COLD THERAPY.

Radiological Cases of the Month

Roger Philip Davies, MB, BS, Kazimierz Kozlowski, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A male infant was born to a 21-year-old mother (gravida 1, para 1) following pregnancy complicated by transient oligohydramnios at 34 weeks. Shortly after birth, an imperforate anus and passage of meconium through the urethra were noted. A defunctioning transverse colostomy was performed with closure of a rectourethral fistula.

Persistent right-upper- and mid-lung pneumonia developed on day 3 of life (Fig 1) and continued without resolution despite three weeks of intensive antibiotic therapy.

Accepted for publication Nov 9, 1987.

From the Department of Radiology, Royal Alexandra Hospital for Children, Sydney, Australia.

Reprint requests to Department of Radiology, Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr B. P. Wood).

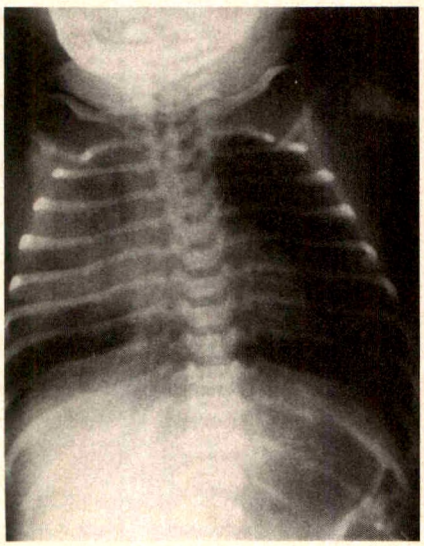


Figure 1.

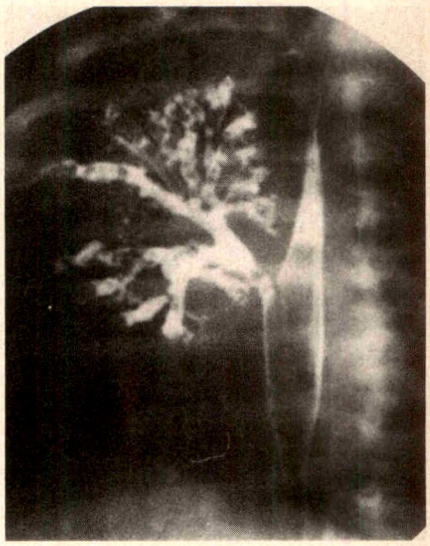


Figure 2.

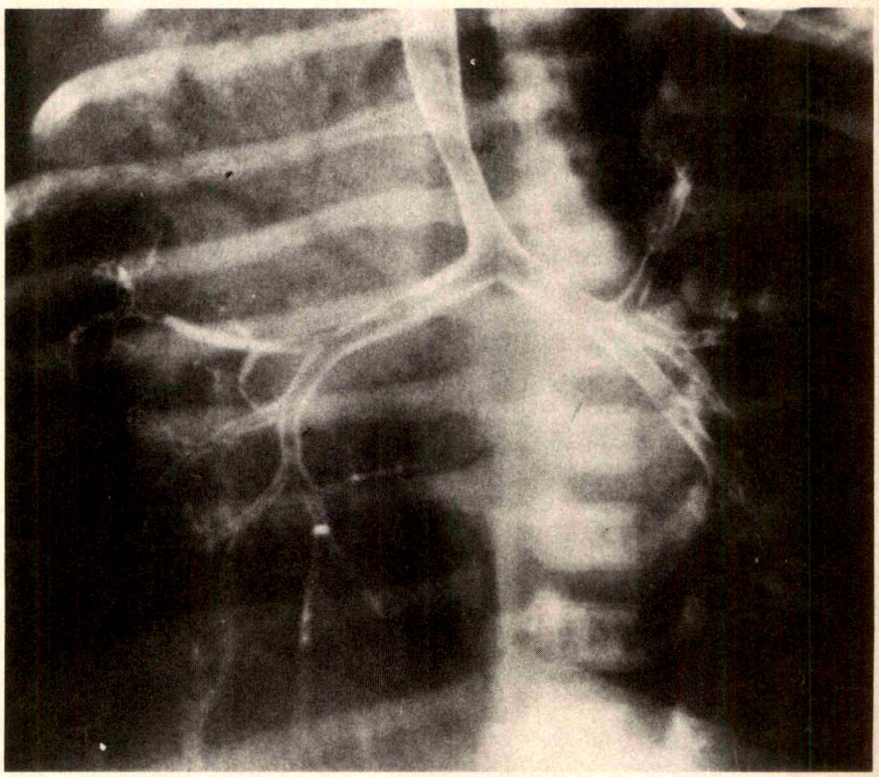


Figure 3.

Denouement and Discussion

Right-Upper-Lobe Esophageal Bronchus (With VATER Anomalies)

Fig 1.—Anteroposterior chest roentgenogram shows extensive consolidation in right-upper- and mid-lung zones. Variable opacities persisted over three-week period after day 3 of life.

Fig 2.—Barium esophagogram shows widely patent right-upper-lobe bronchus originating from midesophagus. There is extensive filling of irregular and ectatic bronchi. Gastroesophageal reflux was noted.

Fig 3.—Bronchogram shows constriction of distal trachea and elongated right bronchus supplying right lower lobe of lung. Air bronchogram can be seen in right upper region of thorax extending from esophagus into consolidated upper lobe.

A barium esophagogram (Fig 2) indicates an anomalous origin from the midthoracic esophagus of a bronchus to the consolidated portion of the right lung. The branching pattern of the bronchi is irregular, and the bronchi are dilated. Free gastroesophageal reflux was present. A bronchogram (Fig 3) shows a smooth tapering constriction of the distal trachea and an elongated, narrowed right bronchus supplying the aerated right lower lobe. An aortogram showed no abnormal systemic supply to the right lung. Continued sepsis necessitated resection of the right upper lobe one week later. Associated abnormalities in this infant consisted of an atrioventricular canal cardiac defect and a mildly hypoplastic right kidney. At 5 months of age, the patient died of overwhelming sepsis.

Approximately 40 cases of unusual communication between the foregut and bronchi have been described. Most cases involve a fistula between the lower esophagus and sequestered left basal lung. Gerle et al[1] reviewed 13 cases in 1968. In ten cases the esophageal bronchus communicated with sequestered or accessory basal lung tissue, and in three cases the fundus of the stomach was the site of communication. In 11 cases the accessory lung tissue was located at the base of the left lung. In many cases of bronchopulmonary foregut malformation with bronchoesophageal fistula, aberrant systemic arterial supply from the aorta is present.[2]

Bronchopulmonary foregut malformations are believed to occur when cells with respiratory potential arise from the primitive esophagus caudal to the site of the usual lung bud or when the lung bud originates from the dorsal esophagus instead of the more ventrally located laryngotracheal tube. These cells enter the neighboring normally developed pulmonary tissue and may connect by a pedicle to the viscus of origin. If this pedicle does not involute, the accessory lung tissue is then in communication with the gastrointestinal tract and a communicating bronchopulmonary foregut malformation results, usually between the distal esophagus and the anomalous lung tissue.[3]

In a number of cases, multiple congenital abnormalities, including complex cardiac, genitourinary, and cloacal anomalies, have been associated with bronchoesophageal communication.

Origin of the right main-stem bronchus[4] and origin of both main-stem bronchi from the esophagus[5] have been described in association with multiple anomalies of the VATER group. In both cases the infant died shortly after birth.

We suggest that when unexplained or persisting pulmonary opacity is seen in a child with congenital abnormalities of the VATER group, specific investigation for a bronchoesophageal fistula should be considered, including barium esophagography, bronchoscopy, or bronchography.

References

1. Gerle RD, Jaretzki A III, Ashley CA, et al: Congenital bronchopulmonary foregut malformation: Pulmonary sequestration communicating with the gastrointestinal tract. *N Engl J Med* 1968;278:1413-1419.
2. Vogt EC: Congenital esophageal atresia. *AJR* 1929;22:463-465.
3. Leithiser RE Jr, Capitanio MA, Macpherson RI, et al: 'Communicating' bronchopulmonary foregut malformations. *AJR* 1986;146:227-231.
4. Bleicher MA, Melmed AP, Bogaerts XV, et al: VATER association and unrecognized bronchopulmonary foregut malformation complicating anesthesia. *Mt Sinai J Med* 1983;50:435-438.
5. Parameswaran A, Krishnaswami H, Walter A: Congenital broncho-oesophageal fistula associated with tracheal agenesis. *Thorax* 1983;38:551-552.

Jonathan Holt Truex, PhD, MD, Teresa L. Silberman, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A 7-year-old boy was seen at follow-up for a Wilms' tumor that had been treated by a right nephrectomy and a regimen of vincristine and dactinomycin at age 3 years. Subsequently, he had no major problems but complained of intermittent abdominal pain and constipation. He had not been taking medication. Nothing exacerbated or relieved the pain, and it spontaneously resolved without intervention. His bowel movements occurred every two to five days. The stool was hard and usually white.

Results of abdominal examination were normal. The hard stool, palpable by rectal examination, was guaiac-negative. The patient was in good health at the time of chest roentgenography. The roentgenograms showed multiple 1- to 3-cm ovoid opacities in the gastrointestinal tract (Figs 1 and 2).

Accepted for publication Nov 9, 1987.
From the Department of Pediatrics, Marshfield Clinic and St Joseph's Hospital, Marshfield, Wis.
Reprint requests to Department of Radiology, Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr B. P. Wood).

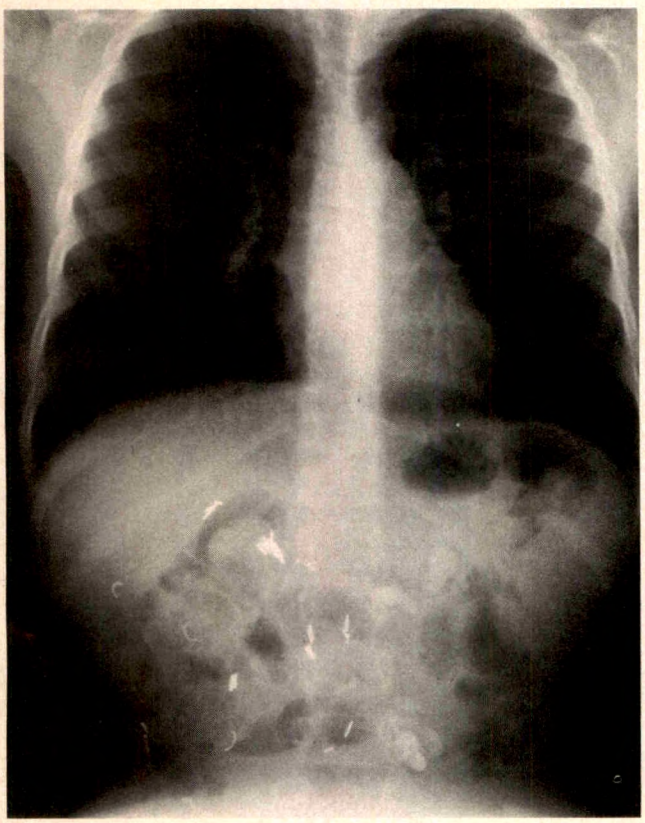


Figure 1.

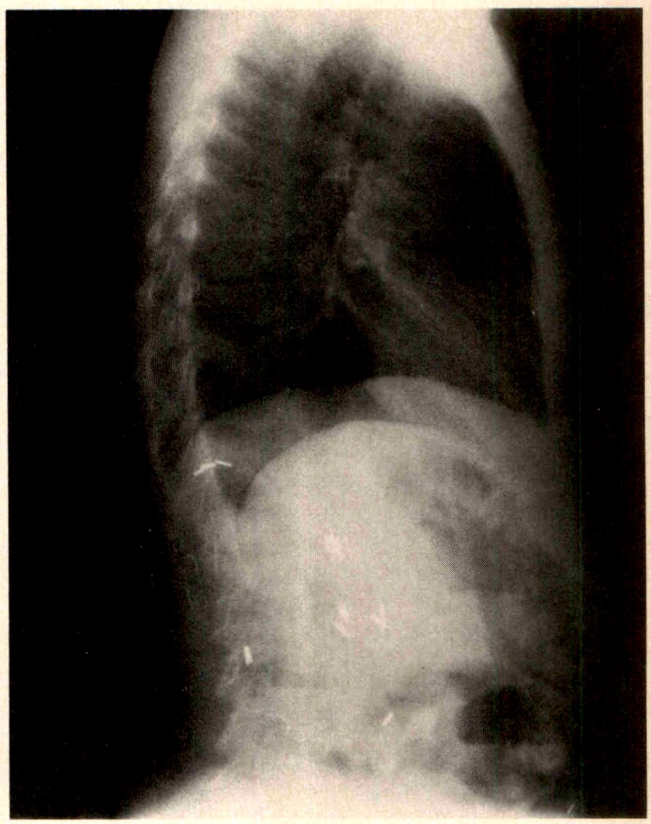


Figure 2.

Denouement and Discussion

Bubble Gum Bezoar

Fig 1.—Chest roentgenogram demonstrates surgical clips in abdomen on right. Multiple 1- to 3-cm ovoid irregular opacities are seen in gastrointestinal tract.

Fig 2.—Lateral chest roentgenogram shows that opacities are in gastrointestinal tract area and are not located in retroperitoneal space.

Fig 3.—Roentgenographic appearance of bubble gum in vinyl examination glove inflated with saline.

The opacities could not be interpreted and were thought to be ingested pills, capsules, or foreign material. The patient's mother was interviewed about diet and habits, and she stated that her son chewed bubble gum and always swallowed it. Several volunteers were enlisted to chew bubble gum for 20 to 30 minutes and to deposit it in a vinyl examination glove inflated with saline; a roentgenogram of the glove was then obtained (Fig 3).

Bubble gum bezoar causes acute or chronic abdominal pain secondary to obstruction.[1] Our patient had chronic constipation and intermittent abdominal complaints for approximately three years. It was fortuitous that the gum opacities, which may not have been related to his chronic abdominal complaints, were seen on the roentgenogram. He was treated with oral mineral oil, and a follow-up roentgenogram showed that the opacities had disappeared.

The latex from several varieties of tropical trees, mainly of the *Sapadillo* genera, is the raw material used for the manufacture of chewing gum. The formula of bubble gum is a proprietary secret, although there are reports of allergy testing to some components.[2,3] Miller[4] described cheilitis secondary to allergy to the essential oils of bubble gum in an executive of a gum manufacturer. He reported the ingredients of bubble gum to be sugar, starch, milk solids, ethyl butyrate, vanilla extract, precipitated chalk, base, cumar resin, erythrocin paste, and essential oils. It is assumed that the precipitated chalk causes the roentgenographic density of swallowed bubble gum. Because chalk is composed of calcium carbonate or calcium sulfate, it is roentgenographically opaque.[5] Our roentgenogram of chewed bubble gum is, admittedly, only circumstantial evidence of the gastrointestinal tract opacities in our patient and we do not propose to conduct a definitive experiment.

Figure 3.

References

1. Cotner M: Fecal impaction due to bubble gum bezoar. *South Med J* 1982;75:775.
2. Georgouras K, Kocsard E: Micropapular sarcoidal facial eruption in a child: Gianotti-type perioral dermatitis. *Acta Derm Venereol* 1978;58:433-436.
3. Perry HO, Deffner NF, Sheridan PJ: Atypical gingivostomatitis. *Arch Dermatol* 1973;107:872-878.
4. Miller J: Cheilitis from sensitivity to oil of cinnamon present in bubble gum. *JAMA* 1941;116:131-132.
5. Gosselin RE, Smith RP, Hodge HC: *Clinical Toxicology of Commercial Products*, ed 5. Baltimore, Williams & Wilkins, 1984, p vi (preface).

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Picture of the Month

Philip R. Cohen, MD, Vincent P. Beltrani, MD, Gregory L. Zalar, MD (*Contributors*);
Murray Feingold, MD (*Section Editor*)

Figure 1.

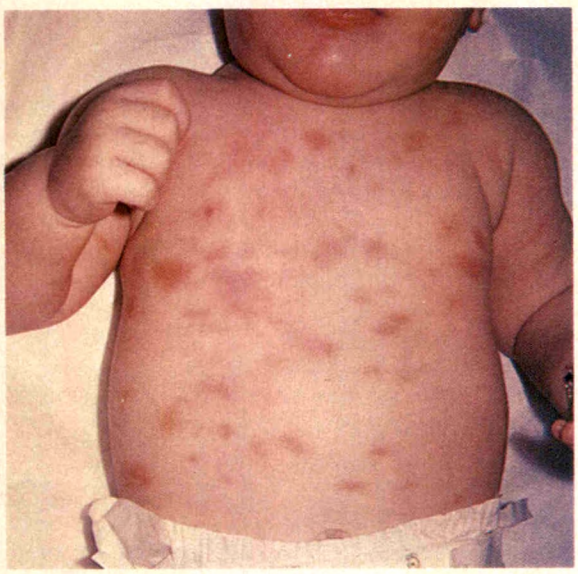


Figure 2.

Figure 3.

The statements listed below are best associated with which of the above figure(s):

(*a*) Transient hematologic and cutaneous eosinophilia.

(*b*) Histologically the skin lesions show vascular dilatation and/or proliferation.

(*c*) The hallmark of the clinical diagnosis is the presence of Darier's sign.

Accepted for publication Aug 5, 1988.
Contributed from St Luke's/Roosevelt Hospital Center, New York.
Reprint requests to National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—Reticulated pattern of telangiectasias on arm of infant with cutis marmorata telangiectatica congenita.

Fig 2.—Multiple, diffusely distributed, red to brown macules, papules, and plaques in infant with generalized urticaria pigmentosa.

Fig 3.—Asymmetrically distributed, irregular streaks and splashes of brown hyperpigmentation on torso of female infant with incontinentia pigmenti.

(*a*) Incontinentia pigmenti, also referred to as Bloch-Sulzberger syndrome, is a genodermatosis with either an autosomal or X-linked dominant (often prenatally lethal in males) inheritance pattern. Characteristic cutaneous features usually, but not always, occur in three successive stages. Present at birth or appearing during early infancy is an erythematous vesiculobullous eruption located primarily on the limbs. This is followed by linear verrucous lesions that are also distributed on the limbs. Subsequently, whorled hyperpigmented lesions (usually asymmetric) involving the torso appear (Fig 3). These pigmented macules gradually spontaneously resolve and the skin usually appears normal by early adulthood. Infrequently, residual atrophic and depigmented lesions are noted on the limbs. A blood leukocytosis with eosinophilia (ranging from 5% to 65%) is often observed that usually coincides with the cutaneous eosinophilia occurring during the vesicular stage. Nearly 80% of patients with incontinentia pigmenti have associated systemic manifestations that include the following: hair (38%) and nail (7%) pathology; dental (65%), ocular (35%), and bony (14%) anomalies; and central nervous system disorders (31%).

(*b*) Common clinical manifestations of cutis marmorata telangiectatica congenita (CMTC) (Fig 1) include persistent cutis marmorata (a reticulated, mottled pattern on the skin that is neither transient nor temperature related), spider nevus–like telangiectasia, and phlebectasia. Less often, ulcers and/or atrophic plaques and other vascular disorders are observed. Skin lesions are usually present at birth, are predominantly distributed on one side of the body (even though bilateral involvement frequently occurs), and often improve most notably within the first two years of life. Histologic features of CMTC can include the following: dilated capillaries, veins, and/or lymphatics; vascular proliferation, fibrosis, and/or thrombosis; perivascular cell infiltration; and/or hyperkeratosis. Cutis marmorata telangiectactica congenita predominantly affects girls (nearly two thirds of patients) and usually occurs sporadically, with the exception of a few hereditary cases with an autosomal dominant mode of inheritance. Various associated congenital physical anomalies, most often limb asymmetry due to hypertrophy or atrophy of an involved extremity, have been reported in approximately 50% of patients with CMTC.

(*c*) Mastocytosis is a heterogeneous disorder in which the clinical features and symptoms are attributable to the infiltration of various tissues by an increased number of mast cells and the substances released by these cells. Approximately 90% of individuals with mastocytosis have involvement limited to the skin, which is referred to as cutaneous mastocytosis, or urticaria pigmentosa (UP). The various types of UP are as follows: localized (mastocytoma); generalized (maculopapular [Fig 2], telangiectasia macularis eruptiva perstans, and erythrodermic or diffuse); and xanthelasmoidea, or pseudoxanthomatous mastocytosis. The skin lesions become erythematous and urticate upon stroking (Darier's sign), which is a major feature of UP. Other frequent symptoms of UP include dermographism, pruritus, and flushing. Systemic mastocytosis can involve the skeletal, gastrointestinal, hematopoietic, and reticuloendothelial systems, or only manifest bone involvement. Rarely, mast cell leukemia is observed. Iodine-containing roentgenographic contrast media and drugs that can activate mast cell degranulation, such as opiates (codeine and morphine), aspirin, several anticholinergic anesthetics, and antiemetics, and certain anti-infectious agents (polymyxin B, amphotericin B, and quinine) should be avoided. The prognosis of mastocytosis is inversely related to the age at onset. When the disease begins before 2 years of age, substantial improvement frequently occurs by puberty; if the onset occurs after 10 years of age, mast cell infiltrates, skin lesions, and symptoms usually persist.

References

1. El-Benhawi MO, George WM: Incontinentia pigmenti: A review. *Cutis* 1988;41:259-262.
2. Carney RG Jr: Incontinentia pigmenti: A world statistical analysis. *Arch Dermatol* 1976;112:535-542.
3. Powell ST, Su WPD: Cutis marmorata telangiectatica congenita: Report of nine cases and review of the literature. *Cutis* 1984;34:305-312.
4. South DA, Jacobs AH: Cutis marmorata telangiectatica congenita (congenital generalized phlebectasia). *J Pediatr* 1978;93:365-949.
5. Stein DH: Mastocytosis: A review. *Pediatr Dermatol* 1986;3:365-375.
6. DiBacco RS, DeLeo VA: Mastocytosis and the mast cell. *J Am Acad Dermatol* 1982;7:709-722.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Avenue, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

CHANGING THE WAY YOU TREAT ASTHMA

"Cromolyn works best when it is used as a 'first line' or primary prophylactic drug before round-the-clock theophylline, adrenergic agents on a continuous basis, or corticosteroids are tried."[1]

INTAL is the only available asthma therapy that effectively blocks[2] both the immediate and late asthmatic response.[2,3,4] Add to this, an antiinflammatory component[4,5], the ability to reduce bronchial hyperreactivity[6] and its unparalleled safety record, and you'll understand why your colleagues are prescribing INTAL for more of their asthmatic patients. As primary therapy, it's ideal for management of mild-to-moderate chronic asthma and exercise-induced asthma.

INTAL®

(cromolyn sodium/FISONS)

Primary therapy, today

Ask your FISONS Representative or call 1-800-223-FISO for Patient Education materials to maximize your success with INTAL (In MA and AK: 617-275-1000).

See adjacent page for brief summary of prescribing information.

INTAL® (cromolyn sodium/FISONS)

Inhaler • Capsules • Nebulizer Solution

DESCRIPTION: INTAL Inhaler (cromolyn sodium inhalation aerosol) is a metered dose aerosol unit for oral inhalation containing micronized cromolyn sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each metered spray delivers to the patient approximately 800 mcg of cromolyn sodium. Each 8.1g canister delivers at least 112 metered sprays (56 doses); each 14.2g canister delivers at least 200 metered sprays (100 doses).

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were: throat irritation or dryness, bad taste, cough, wheeze, nausea.

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

DOSAGE AND ADMINISTRATION: For management of bronchial asthma in adults and children (5 years of age and over) who are able to use the Inhaler, the usual starting dosage is two metered sprays inhaled four times daily at regular intervals.

Patients with chronic asthma should be advised that the effect of INTAL Inhaler therapy is dependent upon its administration at regular intervals, as directed. INTAL Inhaler should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise, exposure to cold dry air or environmental agents, the usual dose is the inhalation of two metered dose sprays shortly, i.e., 10-15 minutes but not more than 60 minutes, before exposure to the precipitating factor.

INTAL INHALER THERAPY IN RELATION TO OTHER TREATMENTS FOR ASTHMA: Non-steroidal agents: INTAL Inhaler should be **added** to the patient's existing treatment regimen (e.g., bronchodilators). When a clinical response to INTAL Inhaler is evident, usually within two to four weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

Corticosteroids: In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of INTAL Inhaler. If the patient improves, an attempt to decrease corticosteroids should be made.

It is particularly important that great care be exercised if for any reason cromolyn sodium is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids.

HOW SUPPLIED: INTAL Inhaler, 8.1g or 14.2g canister, box of one. Supplied with inhalation adapter and patient instructions.

NDC 0585-0675-01 14.2g canister NDC 0585-0675-02 8.1g canister

Store between 2° - 30°C (36° - 86°F). Contents under pressure. Do not puncture or incinerate. Keep out of the reach of children.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for: FISONS CORPORATION
BEDFORD, MA 01730 U.S.A.

By: Riker Laboratories
One Morley Street
Loughborough, England LE11 1EP
Made in England

Revised 7/86
FC 7518B

© Fisons Corporation 1986—All Rights Reserved
INTAL® is a registered trademark of Fisons plc.

References: 1. König P. Cromolyn sodium: Clinical applications and known mechanisms of action. *Hosp Formul* 19(8): 711-17, 1984. **2.** Wilson MC, Larsen GL. Gaining control over the late asthmatic response. *J Respir Dis* 7(8): 51-60, 1986. **3.** Kaliner MA: Late phase reactions. *NER Allergy Proc* 7(3): 236-40, 1986. **4.** Reed CE: New therapeutic approaches in asthma. *J Allergy Clin Immunol* 77(4): 537-43, 1986. **5.** Diaz P, Galleguillos FR, Gonzalez MC, et al: Bronchoalveolar lavage in asthma. The effect of disodium cromoglycate (cromolyn) on leukocyte counts, immunoglobulins, and complement. *J Allergy Clin Immunol* 74(1): 41-48, 1984. **6.** Furukawa CT, Shapiro GG, Bierman CW, et al: A double-blind study comparing the effectiveness of cromolyn sodium and sustained-release theophylline in childhood asthma. *Pediatrics* 74(4): 453-59, 1984.

See package insert for full prescribing information.

FISONS

FISONS CORPORATION
BEDFORD, MA 01730

© Fisons Corporation 1987

FIS-030

Lots of smart companies have high blood pressure control programs.

ITT

Burlington

AT&T

MASSACHUSETTS MUTUAL LIFE INSURANCE COMPANY

Campbell Soup Company

Ford

GM

bloomingdale's

What about yours?

Uncontrolled high blood pressure is a major health problem. About 26 million workdays and billions of dollars are lost each year because of it.

But high blood pressure can be easily detected *and* controlled. Proper treatment, every day, can prevent heart failure, kidney disease, stroke and premature death caused by high blood pressure.

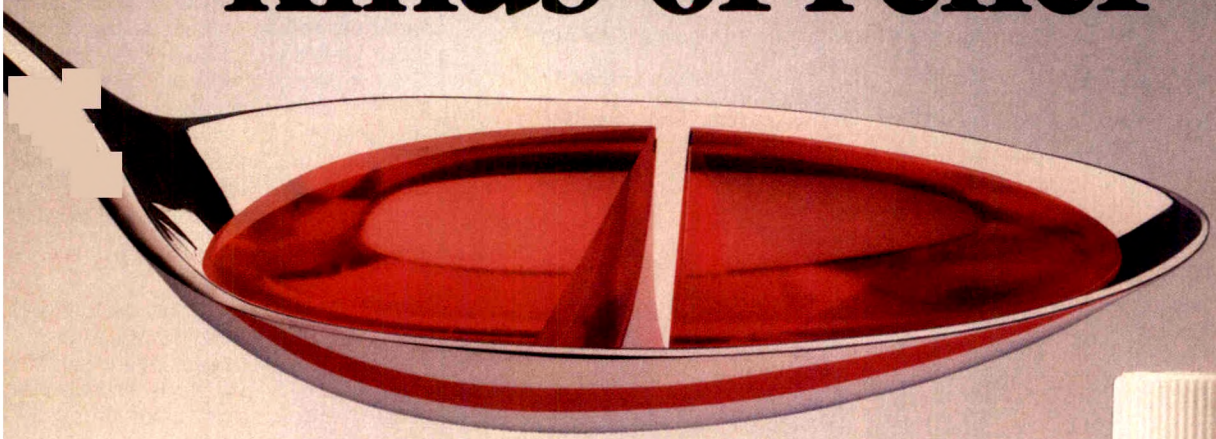
Many companies, large and small, have successful on-the-job high blood pressure programs for their employees and management. Look into it. You can save time and money. And protect your employees' health. To find out the whole story write:

Ms. Judie LaRosa
Worksetting Programs Coordinator
National High Blood Pressure Education Program
Bethesda, MD 20205

High blood pressure. Treat it and live.

National High Blood Pressure Education Program,
National Heart, Lung, and Blood Institute,
U.S. Department of Health and Human Services

Think of it as two kinds of relief



One for colds

Like all Triaminic® products, Triaminicol® starts with a proven decongestant to reduce nasal and sinus congestion.

In addition, Triaminicol contains an effective antihistamine to dry runny noses and itchy, watery eyes.

And one for coughs

To stop coughs cold, Triaminicol contains dextromethorphan, a centrally acting antitussive that is non-narcotic, but equally as effective as codeine.[1-3†]

And Triaminicol does it all *without analgesics or alcohol.*

PEDIATRICIAN #1 RECOMMENDED

Triaminicol®
MULTI-SYMPTOM COLD SYRUP

For the cold with a cough

†Except in severe cough

REFERENCES

1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986; pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharm Times* 1985;51(1):80-90.

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

THE PEDIATRICS BOARD REVIEW COURSE

February 23-28, 1989 – Anaheim
April 6-12, 1989 – Nashville
May 26-31, 1989 – Louisville

Now, your only BOARD REVIEW just before Written and Oral Exams

OBJECTIVES:
- Improve basic and clinical knowledge in pediatrics
- Assist residents and fellows in organizing study
- Prepare candidates to take examinations
- Provide practicing pediatricians with a review and update

METHODS:
- HOME STUDY MATERIALS with a syllabus of questions and answers – and assignments
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

NEONATOLOGY
Growth and Development
Nutrition
Newborn Diseases
Fluids and Electrolytes
Critical Care

IMMUNOLOGY
Immune Physiology
Immunodeficiency
Allergy
Rheumatology

INFECTIOUS DISEASES
Bacterial Infections
Viral Infections
Spirchetes and Richettsia
Mychotic Infections
Parasitic Infections

CARDIOLOGY
Cardiac Evaluation
Cyanotic Diseases
Acyanotic Diseases
Acquired Diseases

GASTROENTEROLOGY
Oral Cavity/Esophagus
Anomalies and Diseases
Malabsorption
Liver and Gall Bladder
Pancreas

NEPHROLOGY
Renal Physiology
Glomerular Diseases
Congenital Uropathies
Urology

ENDOCRINOLOGY
Hypothalamus/Pituitary
Thyroid and Parathyroid
Adrenal Disorders
Gonadal Disorders
Diabetes/Hypoglycemia

HEMATOLOGY-ONC.
Red Cell Disorders
White Cell Disorders
Platelets and Coagulation
Solid Tumors

NEUROLOGY
Convulsive Disorders
Congenital Diseases
Acquired Diseases
Neuromuscular Diseases

PSYCHOLOGY
Psychological Development
Psychiatric Disorders
Child and Drug Abuse
Mental Retardation

GENETICS AND OTHER
Chromosomal Anomalies
Errors of Metabolism
Morphologic Syndromes
Preventive Medicine
Poisoning

OTHER SPECIALITIES
Orthopedics
Dermatology
Opthalmology
Otolaryngology
Pulmonology

Limited Enrollment: PEDIATRICS BOARD REVIEW REGISTRATION

Name _____

Address _____

City/State/Zip _____

Phone _____

For:
- ☐ February 23-28, 1989 – Anaheim
- ☐ April 6-12, 1989 – Nashville
- ☐ May 26-31, 1989 – Louisville
- ☐ Sept. 26-Oct. 1, 1989 – Chicago
- ☐ Check is enclosed for $
- ☐ Please send more information.

Mail today to:

1094 Dawn Lane
P.O. Box 2218
Terre Haute, IN 47802

*"Accommodations were comfortable..."**

GOALS AND LOCATION: The course is held the week before oral and written board exams. Sites are chosen for excellent study and minimal cost of hotel and travel for board candidates. Home study questions will be sent before the course. Your best value is to repeat the seminar for half price the week before both written and oral exams. Topics and faculty are upgraded for each program. Our hotel rates are typically $66 to $80 single and $80 to $98 double. Please wait for instructions before buying travel tickets.

*"...and those little extras...."**

LOWEST AIR FARES: Reliable Travel offers you the lowest air fare – often below super-saver rates. Please call toll-free 1-800-645-6504 ext. 10 and identify yourself with this Osler course for special group fares.

*"...remarkably complete and pleasant."**

PLACEMENT SERVICE: For a practice opportunity write or call (800) 356-7537.

*"...the most education for the money."**

FEES AND C.M.E. CREDITS:
- **C.M.E. Credit: 60 hrs.**
- Practicing Pediatrician: $630
- Residents and Fellows: $420
- Repeating course within 3 years: half price
- **Add 10% for Feb. '89 after Feb. 15, 1989.**
- Attendees not in course hotel add $8/day.
- $50.00 will reserve your position.

*"...home study material was extremely helpful."**

CANCELLATIONS: Refunds subject to $50 fee, will be made until the seminar begins.
- Cancellation after mailing home study material requires retention of half of the fee.

*"I feel [the course] helped me pass the boards."**

INFORMATION:

Joseph H. Selliken Jr., M.D.
THE OSLER INSTITUTE
1094 Dawn Lane, Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

**Comments by participants of our courses*

lished by the American Medical Association

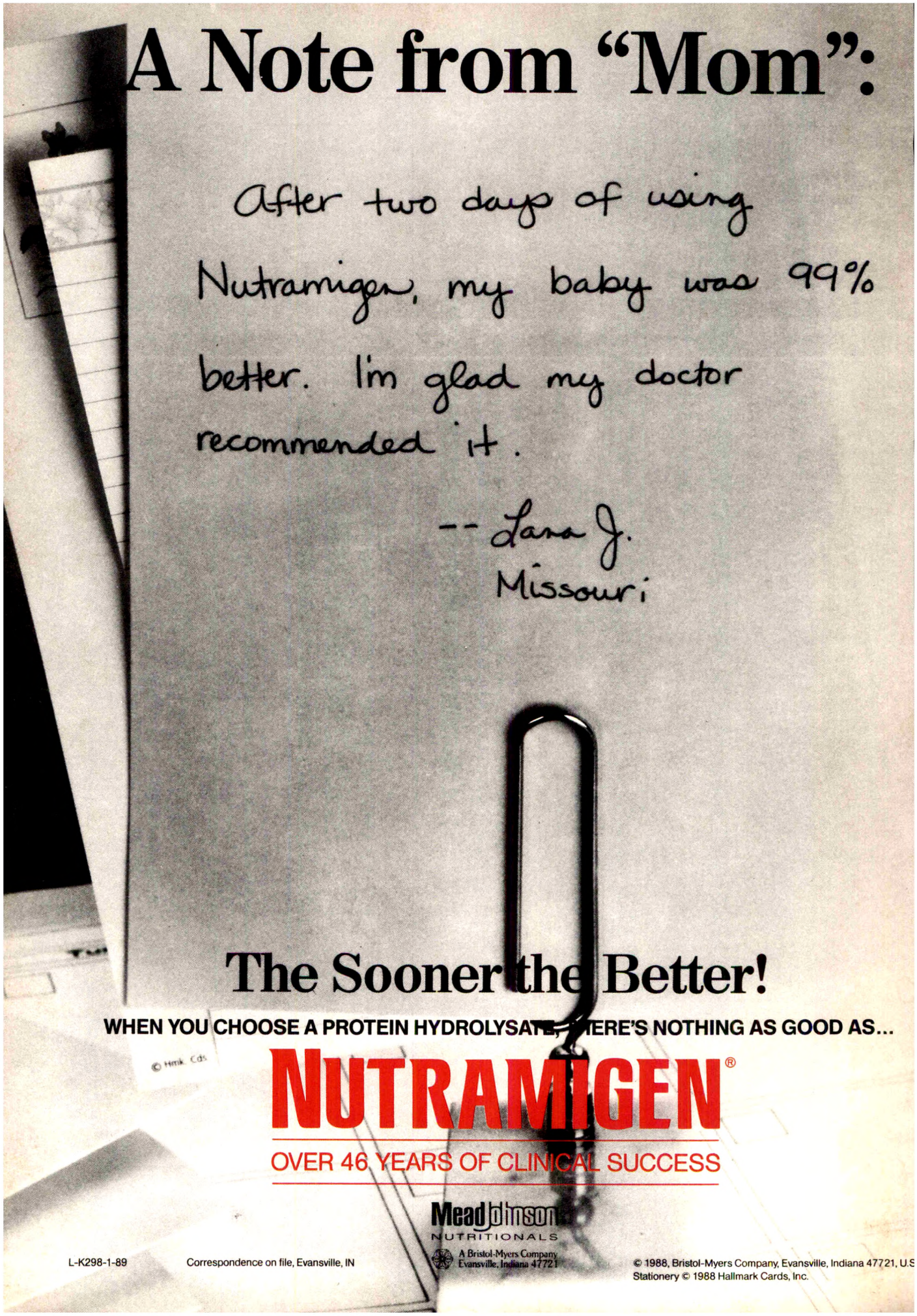
March 1989
Volume 143, Number 3

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

THE PEDIATRIC FORUM		**269**
LEADS FROM THE MMWR		**281**
EDITORIALS: Dexamethasone Therapy for Bacterial Meningitis	*G. H. McCracken, Jr, et al*	**287**
Dexamethasone for Children With Bacterial Meningitis	*S. L. Kaplan*	**290**
Prospective Reimbursement and Pediatric Services	*J. V. Singleton*	**292**
THE EDITORIAL BOARD SPEAKS . . . : Thoughts on Residency Education	*K. B. Roberts*	**294**
ARTICLES: Magnetic Resonance Imaging and Dexamethasone Therapy for Bacterial Meningitis	*M. H. Lebel et al*	**301**
Identification of High-Risk Patients in HIB Meningitis	*N. Gary et al*	**307**
Health Care Financing Policy for Hospitalized Pediatric Patients	*E. Munoz et al*	**312**
Risk Factors and RSV	*E. B. Hayes et al*	**316**
PEDIATRIC PERSPECTIVES: International Adoption	*M. Hostetter et al*	**325**
ARTICLES: Maternal Cigarette Smoking and Cleft Anomalies	*M. J. Khoury et al*	**333**
Recurrent Injuries in Schoolchildren	*W. T. Boyce et al*	**338**
PGE_1 Selectively Reduces Septic Pulmonary Hypertension in Newborn Piglets	*C. Hammerman et al*	**343**
Urinary Tract Infections and Circumcision	*L. W. Herzog*	**348**
REVIEW: Metalloporphyrins in Neonatal Jaundice	*D. K. Stevenson et al*	**353**
ARTICLES: Home Oxygen Therapy	*B. B. Hudak et al*	**357**
Gastrointestinal Milk Intolerance of Infancy	*S. Berezin et al*	**361**
Cardiac Care in Down Syndrome	*D. S. Schneider et al*	**363**
Suggestive 'Ectopic' Pituitary Gland	*A. W. Root et al*	**366**
Effects of Theophylline on Behavior and Learning in Children With Asthma	*L. Rappaport et al*	**368**
EDUCATIONAL INTERVENTIONS: Educational Booklet and Total Parenteral Nutrition	*L. Laine et al*	**374**
SPECIAL FEATURES: Radiological Case of the Month	*A. L. Weisberg et al*	**379**
Picture of the Month	*M. E. Rimsza et al*	**381**

***AJDC* Is Moving . . .**

As of April 1989, the AJDC editorial office will be located at Tulane University. After April 19, please address all correspondence, manuscripts, and inquiries to Vincent A. Fulginiti, MD, Editor, *AJDC*, Dean's Office, Room 1529, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; (504) 584-1989.


A Note from "Mom":
After two days of using Nutramigen, my baby was 99% better. I'm glad my doctor recommended it.
-- Lara J.
Missouri
The Sooner the Better!
WHEN YOU CHOOSE A PROTEIN HYDROLYSATE, THERE'S NOTHING AS GOOD AS...
NUTRAMIGEN®
OVER 46 YEARS OF CLINICAL SUCCESS
Mead Johnson
NUTRITIONALS
A Bristol-Myers Company
Evansville, Indiana 47721
L-K298-1-89
Correspondence on file, Evansville, IN
© 1988, Bristol-Myers Company, Evansville, Indiana 47721, U.S
Stationery © 1988 Hallmark Cards, Inc.

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOL 143 NO. 3 MARCH 1989

Copyright © 1989 by the American Medical Association

Monthly Circulation >44 500
Also published in French

THE PEDIATRIC FORUM

269 **Editor's Note . . . The Epidemic Hysteria Dilemma** Matthew L. Cartter, MD; Patricia Mshar; Harold Burdo, MPH, Hartford, Conn . . . **Cutis Verticis Gyrata and Chromosomal Abnormalities** Marini Romana, MD, Marco Cappa, MD, Rome, Italy; Giovanni Neri, MD, Chieti, Italy . . . **A Benign Cause of Intermittent Bradycardia of Prematurity** Shimon Reif, MD; Nechemia Keisar, MD; Shimon Barak, MD; Boaz Mulbauer, MD, Tel-Aviv, Israel . . . **Beriberi in a Southeast Asian Adolescent** Karen Vrchota, MD, Charles N. Oberg, MD, Minneapolis, Minn; Kevin N. Harris, MD, Hanover, NH . . . **Injury Prevention: Drowning** Barbara Smith, MD, Tucson, Ariz, Dorothy Noyes, MPH, PhD, New York, NY . . . **Bone Mineral Status in Hypopituitarism** Osamu Arisaka, MD; Madoka Arisaka, MD; Atsuto Hosaka, MD; Keijiro Yabuta, MD, Tokyo, Japan . . . **Occult Bacteremia in Children With Simple Febrile Seizures** Daniel E. Torphy, MD, William A. Bonadio, MD, Milwaukee, Wis; James M. Chamberlain, MD, Washington, DC; Richard L. Gorman, MD, Baltimore, Md

281 **LEADS FROM THE MMWR**

EDITORIALS

287 **Dexamethasone Therapy for Bacterial Meningitis in Infants and Children**
George H. McCracken, Jr, MD, Marc H. Lebel, MD, Dallas, Tex

290 **Dexamethasone for Children With Bacterial Meningitis**
Sheldon L. Kaplan, MD, Houston, Tex

292 **Prospective Reimbursement and Pediatric Services**
J. Verne Singleton, Tucson, Ariz

THE EDITORIAL BOARD SPEAKS . . .

294 **Thoughts on Residency Education, 1969-1989**
Kenneth B. Roberts, MD, Worcester, Mass

ARTICLES

301 **Magnetic Resonance Imaging and Dexamethasone Therapy for Bacterial Meningitis**
Marc H. Lebel, MD; M. Jean Hoyt, RN; David C. Waagner, MD; Nancy K. Rollins, MD; Terese Finitzo, PhD; George H. McCracken, Jr, MD, Dallas, Tex

307 **Clinical Identification and Comparative Prognosis of High-Risk Patients With *Haemophilus influenzae* Meningitis**
Nancy Gary, MS; Nancy Powers, PsyD; James K. Todd, MD, Denver, Colo

312 **Health Care Financing Policy for Hospitalized Pediatric Patients**
Eric Munoz, MD, MBA, New Hyde Park, NY; Donald Chalfin, MD, Stonybrook, NY; Jonathan Goldstein, MPA; Rudy Lackner, MD; Katherine Mulloy, AS; Leslie Wise, MD, New Hyde Park, NY

Continued on p 263.

EDITORIAL BOARD

Editor

Vincent A. Fulginiti, MD
American Journal of Diseases of Children
PO Box 43700
Tucson, AZ 85733
(602) 626-4304

Associate Editors

James J. Corrigan, Jr, MD
Tucson, Ariz

Alan D. Bedrick, MD
Tucson, Ariz

Book Review Editor

Peggy C. Ferry, MD
Tucson, Ariz

Administrative Assistant

Joann M. Quane
Tucson, Ariz

Secretary

Laura Martin
Tucson, Ariz

Hugh D. Allen, MD, Columbus, Ohio
Milton I. Arnold, MD, Los Angeles, Calif
Richard W. Blumberg, MD, Atlanta, Georgia
Ben H. Brouhard, MD, Cleveland, Ohio
George W. Brown, MD, Los Lunas, NM
Beverly B. Dahms, MD, Cleveland, Ohio
Murray Feingold, MD, Boston, Mass
Patricia Ferrieri, MD, Minneapolis, Minn
Laurence Finberg, MD, Brooklyn, NY
Boyd W. Goetzman, MD, PhD, Davis, Calif
John D. Johnson, MD, Albuquerque, NM
James P. Keating, MD, St Louis, Mo
Elizabeth R. McAnarney, MD, Rochester, NY
Dan G. McNamara, MD, Houston, Tex
Beverly C. Morgan, MD, Orange, Calif
Henry L. Nadler, MD, Chicago, Ill
Robert Penny, MD, Los Angeles, Calif
Albert W. Pruitt, MD, Augusta, Ga
Kenneth B. Roberts, MD, Worcester, Mass
Barton D. Schmitt, MD, Denver, Colo
E. Richard Stiehm, MD, Los Angeles, Calif
William B. Strong, MD, Augusta, Ga
Beverly P. Wood, MD, Rochester, NY

THE COUGH STOPS HERE.

Stops coughs cold.

Triaminic-DM® stops coughs cold with centrally acting dextromethorphan. It's as effective as codeine, without codeine's side effects.[1-3†]

A proven decongestant clears stuffy noses and reduces phlegm that runs down the throat, causing irritation.

Without alcohol.

Triaminic-DM is 100% alcohol free. No unnecessary ingredients. No drowsiness.

See what's new!
Booth 121
AAP Spring Meeting
March 11-16
Orlando, Florida

PEDIATRICIAN #1 RECOMMENDED

Triaminic-DM®
COUGH FORMULA

Stops coughs. Without alcohol.

†Except in severe cough

References:
1. Decongestant, Cough and Cold Preparations in *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986, pp 374 and 384.
2. Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. *J Respir Dis* 1987;8(1):20-34.
3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharmacy Times* 1985;51(1):80-90.

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

Continued from p 261.

316 Respiratory Syncytial Virus Outbreak on American Samoa
Edward B. Hayes, MD; Eugene S. Hurwitz, MD; Lawrence B. Schonberger, MD; Larry J. Anderson, MD, Atlanta, Ga

PEDIATRIC PERSPECTIVES

325 International Adoption
Margaret Hostetter, MD, Dana E. Johnson, MD, PhD, Minneapolis, Minn

ARTICLES

333 Does Maternal Cigarette Smoking During Pregnancy Cause Cleft Lip and Palate in Offspring?
Muin J. Khoury, MD, PhD; Marco Gomez-Farias, MD, MPH; Joseph Mulinare, MD, MSPH, Atlanta, Ga

338 Recurrent Injuries in Schoolchildren
W. Thomas Boyce, MD, San Francisco, Calif; Sue Sobolewski, RN, MPH, Tucson, Ariz

343 Prostaglandin E_1 Selectively Reduces Group B β-Hemolytic Streptococci–Induced Pulmonary Hypertension in Newborn Piglets
Cathy Hammerman, MD; Mary Jane Aramburo, MD; Jung-Hwan Choi, MD; Val Hill, Chicago, Ill

348 Urinary Tract Infections and Circumcision
Lynn W. Herzog, MD, MPH, Boston, Mass

REVIEW

353 The Use of Metalloporphyrins for the Chemoprevention of Neonatal Jaundice
David K. Stevenson, MD; Pamela A. Rodgers, PhD; Hendrik J. Vreman, PhD, Stanford, Calif

ARTICLES

357 Home Oxygen Therapy for Chronic Lung Disease in Extremely Low-Birth-Weight Infants
Bonnie B. Hudak, MD; Marilee C. Allen, MD; Mark L. Hudak, MD; Gerald M. Loughlin, MD, Baltimore, Md

361 Gastrointestinal Milk Intolerance of Infancy
Stuart Berezin, MD; Steven M. Schwarz, MD; Mark Glassman, MD; Marianna Davidian, MD; Leonard J. Newman, MD, Valhalla, NY

363 Patterns of Cardiac Care in Infants With Down Syndrome
Daniel S. Schneider, MD; Kenneth G. Zahka, MD; Edward B. Clark, MD; Catherine A. Neill, MD, FRCP(LOND); and the Baltimore-Washington Infant Study Group, Baltimore, Md

366 Subhypothalamic High-Intensity Signals Identified by Magnetic Resonance Imaging in Children With Idiopathic Anterior Hypopituitarism
Allen W. Root, MD; Carlos R. Martinez, MD; Lawrence R. Muroff, MD, Tampa, Fla

368 Effects of Theophylline on Behavior and Learning in Children With Asthma
Leonard Rappaport, MD; Hugh Coffman, PhD; Richard Guare, PhD; Terrance Fenton, EdD; Christopher DeGraw, MD; Francis Twarog, MD, PhD, Boston, Mass

Continued on p 265.

The AMERICAN JOURNAL OF DISEASES OF CHILDREN is a member of the consortium of AMA journals listed below. The Archives reaches more than 41 500 readers in 85 countries each month. The complete text of all AMA journals is available on the MEDIS data base from Mead Data Central, Dayton, Ohio.

JAMA The Journal of the American Medical Association

AJDC American Journal of Diseases of Children

archives of
Dermatology

archives of
General Psychiatry

archives of
Internal Medicine

archives of
Neurology

archives of
Ophthalmology

archives of
Otolaryngology-Head & Neck Surgery

archives of
Pathology & Laboratory Medicine

archives of
Surgery

James H. Sammons, MD, Executive Vice-President

James S. Todd, MD, Senior Deputy Executive Vice-President

Kenneth E. Monroe, Deputy Executive Vice-President

Theodore R. Chilcoat, Jr, Assistant Executive Vice-President

M. Roy Schwarz, MD, Assistant Executive Vice-President

George D. Lundberg, MD, Vice-President, Scientific Information

John T. Baker, Vice-President, Publishing

Norman D. Richey, Director, Publication Production and Printing Division

Lee A. Parent, Director, Circulation-Fulfillment Division

Dennis Joseph Dennehy, Director, Advertising Sales and Promotion Services Division

Thomas J. Carroll, Director, Department of Advertising Communication

Raymond Christian, Director, Advertising Services Department

Bicillin® C-R 900/300

(penicillin G benzathine and penicillin G procaine suspension)

Because compliance doesn't have t
depend on who's tending the tots.

WYETH-AYERST LABORATORIES™

©1987, Wyeth-Ayerst Laboratories

Philadelphia, PA 19101

PUBLICATION STAFF
Offices: 535 N Dearborn St
Chicago, IL 60610

Managing Editor and Director, AMA Specialty Journals:
Michael D. Springer

Associate Editor:
Julie Foreman

Production Manager:
Marlene M. Hinsch

Assistant Production Manager:
John R. Sayban

Editorial Processing Manager:
Cheryl Iverson

Assistant Editorial Processing Manager:
Paula Glitman

Permissions and Graphic Design Manager:
Dennis J. Shipley

Staff Assistants:
Diane Darnell
Bonnie Van Cleven

Copy Editing:
Patricia A. Predey (Supervisor)
Vickey Golden (Free-lance Coordinator)
Paul Frank (Senior Copy Editor)
Stephen Borysewicz
John Radanovich

Production Supervisors:
Betty Frigerio (Advertising)
Thomas J. Handrigan (Illustrations)
Elizabeth Petrikenas (Proofreading)
Mary C. Steermann (Editorial)
JoAnne Weiskopf (Layout)

Proofreading:
Teresa H. Omiotek
Richard T. Porter
Jennifer Reiling
Barbara Wojtowicz

Art and Senior Production Assistants:
Melinda Arcabos
Cari Biamonte
Laura Bleiler
Karen Branham
Cynthia Gelper
Jerri Hall-Gortowski
Anita Henderson
Debra Lucas
Kimberly McCormick
Juliana K. Mills
Dorothy Patterson
Susan Price
E. Ruth White
Ellen Yoshihara

Production Assistant:
Darlene E. Filips

Editorial Assistant:
Jean Schaffner

Department of Scientific and Socioeconomic Indexing:
Norman Frankel (Director)
George Kruto
Susan McClelland
Mary Kay Tinerella

Please address communications concerning accepted or published communications to AMA Specialty Journals, 535 N Dearborn St, Chicago, IL 60610.

EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

Continued from p 263.

EDUCATIONAL INTERVENTIONS

374 An Educational Booklet Diminishes Anxiety in Parents Whose Children Receive Total Parenteral Nutrition
Laura Laine, MEd, RD; Robert J. Shulman, MD; Kay Bartholomew, MPH; Pat Gardner, RN; Theresa Reed, RN; Sally Cole, RN, Houston, Tex

SPECIAL FEATURES

379 Radiological Case of the Month
Andrew L. Weisberg, MD;
Jack O. Haller, MD (*Contributors*), Brooklyn, NY;
Beverly P. Wood, MD (*Section Editor*), Rochester, NY

381 Picture of the Month
Mary E. Rimsza, MD (*Contributor*), Phoenix, Ariz;
Murray Feingold, MD (*Section Editor*), Brighton, Mass

BOOK REVIEW

Ambulatory Pediatric Care (Dershewitz, ed) Reviewed by Gerald B. Hickson, MD, Nashville, Tenn (p 321)

276 INDEX TO ADVERTISERS

INSTRUCTIONS FOR AUTHORS (See February 1989 issue, p 136)

***AJDC* Is Moving . . .**

As of April 1989, the AJDC editorial office will be located at Tulane University. After April 19, please address all correspondence, manuscripts, and inquiries to Vincent A. Fulginiti, MD, Editor, *AJDC*, Dean's Office, Room 1529, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; (504) 584-1989.

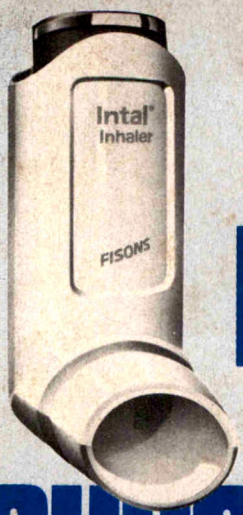
AJDC, American Journal of Diseases of Children (ISSN 0002-922X) is published monthly by the American Medical Association, 535 N Dearborn St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

SUBSCRIPTION RATES—The subscription rates for the American Journal of Diseases of Children are as follows: $48 for one year, $81 for two years in the United States and US Possessions; all other countries, one year, $58; two years, $101 for surface delivery. (For expedited air delivery to most countries, add $15 surcharge for one year subscription, $30 for two years.) Rates for subscriptions for delivery to Japan or South Korea are available through exclusive agents—contact the publisher. ***Special rates for residents and medical students in the United States and US Possessions are available.*** Address inquiries to the American Medical Association, Circulation and Fulfillment Division, 535 N Dearborn St, Chicago, IL 60610. Phone: (312) 280-7168.

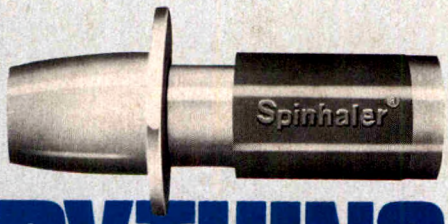
CHANGE OF ADDRESS—POSTMASTER, send all address changes for AJDC, American Journal of Diseases of Children to Subscription Department, 535 N Dearborn St, Chicago, IL 60610. Notification of address change must be made at least six weeks in advance, include both old and new addresses, a recent mailing label, and your new zip code.

ADVERTISING OFFICES: Eastern: 600 Third Ave, Suite 3700, New York, NY 10016 (**Manager:** Robert C. Corcoran [212-867-6640]; **Representative:** Phillip B. Altamore); **Midwest/Farwest:** 535 N Dearborn St, Chicago, IL 60610 (**Manager:** Thomas J. Carroll [312-280-7182]; **Representatives:** John P. Cahill, Midwest; Daniel T. Mjölsness, Farwest)

Advertising Principles: Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.



FORM AND SUBSTANCE ARE EVERYTHING



INTAL®

(cromolyn sodium/FISONS)

Available as

INTAL Inhaler **INTAL Capsules** with Spinhaler® Turbo-Inhaler **INTAL Nebulizer Solution**

FISONS

FISONS CORPORATION
BEDFORD, MA 01730

FIS-031

HIGH STANDARDS

The AMA's Ninth Annual Health Reporting Conference featuring TV/Radio Reporting and Spokesperson Training

April 13-16, 1989
Boston, Massachusetts

This conference is for physicians now on the air and for those who wish to break into broadcasting. Workshops are designed to provide skills enhancement for physician broadcasters and physician spokespersons at all levels. Health Reporting Conference training enables physician broadcasters and spokespersons to achieve and maintain high standards as medical reporters and spokespeople.

Workshops offer:
- —Hands-on television and radio studio experience
- —Broadcast writing, production and videotape editing workshops
- —Interviewing techniques
- —How to break into broadcasting, cable or narrowcasting
- —Voice training, make-up, contract negotiations
- —Platform speaking skills

A Unique Opportunity for
- —Networking
- —Critiques
- —Peer discussions

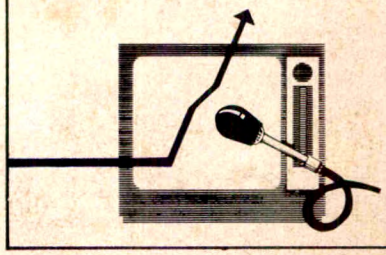
Fee Information

Fees: $590/AMA Members
$750/Non-Members
$200/Residents, Students
$250/Optional Day

Register for speakers training, beginning, intermediate or advanced broadcasting courses. Electives are open to all participants. Complete registration information is available by calling: 312/645-5102.

AMA
AMERICAN MEDICAL ASSOCIATION

Pfizer Laboratories and **Roerig**
Divisions of Pfizer Pharmaceuticals



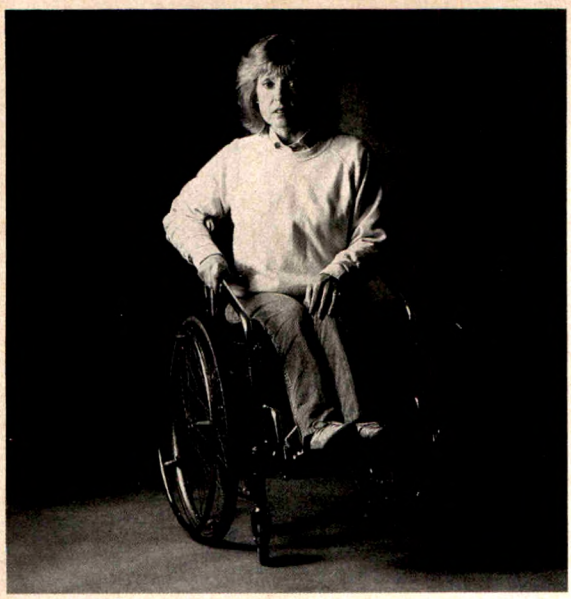
When I was a child there was no Orimune®

Poliovirus Vaccine Live, Oral Trivalent

Jackie DiLorenzo of Hastings-on-Hudson, New York, contracted polio in 1950, before a vaccine became available. She spent ten years in rehabilitation, during which time she underwent nine operations on her spine, legs and feet. Jackie currently lives in a house adapted for wheelchair living.

Lederle Biologicals Protecting Families Through Immunization®

Please see following page for brief summary of prescribing information.



When I was a child there was no Orimune®

Proven in Millions of US Patients

ORIMUNE was the first live, oral, trivalent polio vaccine. No other oral polio vaccine has done more to help eradicate wild poliovirus in the US. Approximately 500 million doses have been distributed to date.

Proven Safety Record*

Lederle takes every precaution during production and testing to ensure the safety of ORIMUNE. This dedication is evident by our 25-year safety record.

Uninterrupted Supply

Lederle has consistently met the nation's needs for oral polio vaccine for about 25 years. In fact, when all other US manufacturers discontinued the production of oral polio vaccine, Lederle has remained committed to this essential product and to the health of America's children.

Available in Single-Doses

ORIMUNE is available in convenient, unit-dose DISPETTES® to help assure dosage accuracy and avoid the risk of contamination.

*See adverse reactions section of brief summary

Orimune®
Poliovirus Vaccine Live, Oral Trivalent

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

A Brief Summary

Please see package insert for full description, directions for use, and references.

INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*
CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev. 8/86

Lederle Biologicals
® Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470

© 1988 Lederle Laboratories

603-8

The Pediatric Forum

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

Editor's Note

In this issue the first article(s) edited in accordance with our new style appears. For our current style, consult *American Medical Association Manual of Style*, eighth edition, available from the publisher, Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202; 1-800-638-0672.

The Epidemic Hysteria Dilemma

Sir:—Outbreaks of illness among schoolchildren can be dramatic and perplexing events for school officials, physicians, and public health professionals. Such outbreaks can pose pitfalls for their investigators, especially when the diagnosis of epidemic hysteria is considered. In 1986, we were asked to investigate an outbreak of possible foodborne illness in sixth-grade students at a school in Connecticut. The outbreak occurred while the students were practicing the school song for graduation ceremonies. At least 39 of the 72 students became ill over a half-hour period. Symptoms most frequently reported were abdominal pain (74%), headache (67%), sweating (64%), weakness (62%), and dizziness (54%). The physical examination findings were normal and symptoms resolved for most within three hours of illness onset. Three teachers who had eaten food served at the party became nauseated later in the afternoon. Further questioning suggested that their illnesses may have been associated with the perception of having been exposed. The epidemiologic investigation revealed that students who had eaten chocolate cake at the graduation day lunch were more likely to become ill than students who did not (relative risk = 2.0, 95% confidence limits = 1.3 to 3.0, $P<.01$). The review of food-handling procedures and laboratory tests of the cake and other foods failed to identify problems with preparation or a bacterial or chemical cause of illness.

The rapid onset of illness and resolution of symptoms and the absence of vomiting and diarrhea made it difficult to attribute this outbreak to a known bacterial or toxic cause of food poisoning. Still, we felt an obligation to rule out possible physical causes of the outbreak. Because the outbreak had some of the features of mass psychogenic illness, our "in-house" assessment was that much of the illness may have been due to epidemic hysteria.[1] Of particular importance was the lack of evidence of a continuing or more widespread threat to public health. This was the key message that we wanted to convey to the public.

The press reported that we were considering the diagnosis of epidemic hysteria on the same day that students were given the food history questionnaires. Our unanticipated public discussion of this diagnosis was done largely without the results of the data analysis, which was completed a week after the outbreak. Despite our assurances that the symptoms of psychogenic illness were real, some parents insisted that we had accused their children of faking symptoms and that a "stigma" had been put on their children. Levine[2] has suggested that the treatment of mass hysteria should include informing patients and the public of the suspected psychological cause of the illness. Our experience suggests that with such notification, the diagnosis can become part of the problem and the public relations aspect of an investigation can easily become the primary focus of activity.

Differentiating a foodborne outbreak from epidemic hysteria has important implications for clinical treatment and for public health control measures. If done early enough, an epidemiologic investigation can help focus control measures, especially during a foodborne outbreak. If done after an outbreak is over, an epidemiologic investigation can help in the review of professional decisions. Our investigation revealed an association between eating chocolate cake and illness, an association that we found difficult to explain and that was for us analogous to finding an unexpected cause of death at autopsy.

Some authors have cautioned against extensive epidemiologic investigations when epidemic hysteria is considered because of the tendency of such investigations to prolong public concern.[1,3] Clearly, the public relations aspect of the investigation must be handled carefully to avoid public misunderstanding. In retrospect, psychiatric consultation might have been helpful in managing the outbreak, both to examine children for positive psychologic data and to endorse the diagnosis of epidemic hysteria. Outbreaks similar to the one that we investigated happen often enough that clinicians and public health professionals need to become better acquainted with the science and art of dealing with epidemic hysteria. It is hoped that knowledge and experience once shared will lead to better ways of managing such episodes.

MATTHEW L. CARTTER, MD
PATRICIA MSHAR
HAROLD BURDO, MPH
State of Connecticut
Department of Health Services
150 Washington St
Hartford, CT 06106

1. Small EW, Borus JR: Outbreak of illness in a school chorus: Toxic poisoning or mass hysteria? *N Engl J Med* 1982;308:632-635.
2. Levine RJ: Mass hysteria: Diagnosis and treatment in the emergency room, editorial. *Arch Intern Med* 1984;144:1944-1945.
3. Epidemic hysteria, editorial. *Br Med J* 1979;2:408.

Cutis Verticis Gyrata and Chromosomal Abnormalities

Sir:—In the article by Felding and Feingold,[1] published in the March 1988 issue of *AJDC*, the last sentence seems to imply that there are no chromosomal abnormalities observed in cases of cutis verticis gyrata (CVG). We recently treated a patient with Turner's syndrome (karyotype: 45,X) who exhibited such an anomaly.

Patient Report.—The patient was born of two drug-addicted parents and had a birth weight of 2350 g (less than the third percentile), a length of 45 cm (less than the third percentile), Apgar scores of 7 and 8 at 1 and 5 minutes, respectively, and congenital lymphedema. When we saw her at 2½ years of age, her height was 80.7 cm (−2 SDs), she weighed 10.6 kg (third percentile), and her head circumference was 47 cm (tenth percentile). The patient had low-set, posteriorly angulated ears, downward-slanted palpebral fissures, epicanthal folds, a short webbed neck, a low posterior hairline, and hyperconvexity of the fingernails. The left temporal area of the scalp

Left temporal area of scalp of patient with Turner's syndrome, with corrugated appearance typical of cutis verticis gyrata.

presented a corrugated appearance typical of CVG (Figure). Examination of a biopsy specimen from this area disclosed normal skin with connective-tissue hypertrophy.

A computed tomographic scan of the brain showed no abnormalities. Results of a heart and kidney evaluation were normal. Endocrinologic studies disclosed high levels of follicle-stimulating hormone and luteinizing hormone. A complete screening for congenital infections, including TORCH, syphilis, and human T-cell lymphotrophic virus type III, gave normal results.

Comment.—We have described a nonhereditary case of CVG in a patient with a chromosomal anomaly and no evidence of chronic inflammation or other conditions that have been proposed as causes of CVG.[1] Given the presence of congenital lymphedema, we propose that this may have been the cause of CVG in our patient.

Marini Romana, MD
Marco Cappa, MD
Department of Pediatric Endocrinology
Ospedale Pediatrico Bambino Gesu
Istituto di ricerca scientifica
Piazza S Onofrio 4
00165, Rome, Italy
Giovanni Neri, MD
Istituto di Biologia Genetica
Universitá degli studi "G. D'Annunzio"
di Chieti
66100 Chieti, Italy

1. Felding I, Feingold M: Cutis verticis gyrata. *AJDC* 1988;142:305-306.

A Benign Cause of Intermittent Bradycardia of Prematurity

Sir:—Intermittent bradycardia, a common problem in preterm infants, develops in approximately 25% of infants of less than 32 weeks' gestation.[1] The causes vary from life-threatening conditions, such as septicemia, intracranial injuries, and metabolic disturbances, to relatively benign ones, such as idiopathic apnea and bradycardia of prematurity.[2]

Recently, we treated an infant who was born in an uncomplicated delivery after 30 weeks' gestation, weighing 1200 g. Apgar scores at one and five minutes were 8 and 9, respectively. At the age of 96 hours, the infant began having attacks of bradycardia. Prior to this incident, he had been receiving phototherapy for indirect hyperbilirubinemia.

The evaluation included a determination of serum levels of glucose, calcium, and electrolytes; a determination of arterial blood gases; a sepsis work-up; and an imaging of the brain cavities to rule out ventricular hemorrhage. All test results were negative or normal, and theophylline therapy was instituted. Nevertheless, the bradycardiac episodes continued. On the sixth day of life, due to the indirect hyperbilirubinemia, we performed an exchange transfusion. The procedure was performed without eye shields and the bradycardia stopped. On the assumption that the tight eye shield might be the cause of the bradycardia, we reinstituted it, and indeed, the bradycardia reappeared.

It is known that vagal tonicity is increased in premature infants.[3] This is best demonstrated by inserting a nasogastric tube or measuring rectal temperatures. We should consider that idiopathic bradycardia can be attributed to eyeball pressure, which is no less a parasympathetic stimulus.

Shimon Reif, MD
Nechemia Keisar, MD
Shimon Barak, MD
Boaz Mulbauer, MD
Departments of Pediatrics and Neonatology
Tel-Aviv Medical Center
Sackler Faculty of Medicine
Tel-Aviv University
Israel

1. Jones RAK: Apnea of immaturity. *Arch Dis Child* 1982;57:761-765.
2. Daily WJR, Klaus M, Meyer HBP: Apnea in premature infants: Monitoring, incidence, heart rate changes and an effect of environmental temperature. *Pediatrics* 1969;43:510-518.
3. Apitzer AR, Fox WW: Infant apnea. *Pediatr Clin North Am* 1986;3:561-581.

Beriberi in a Southeast Asian Adolescent

Sir:—Beriberi, or thiamine (B_1) deficiency, is commonly believed to be extremely rare in the United States today except among alcoholics. We treated a Southeast Asian (Hmong) youth with multisystem organ failure whose symptoms and metabolic abnormalities resolved after administration of thiamine. The low level of suspicion delayed the diagnosis, highlighting the necessity to incorporate nutritional assessment into the management of our patients.

Patient Report.—A 17-year-old Hmong refugee boy had a one-week history of anorexia, emesis, epigastric pain, weakness, dizziness, calf tenderness, and lower-extremity pain. He was moderately dehydrated and was admitted to the hospital for rehydration. The Hmong are a Southeast Asian ethnic group who reside in the northern mountainous regions of Laos and Thailand. The patient had been in the United States for seven years, and had 11 previous admissions for dehydration secondary to nausea and vomiting that initially was thought to be secondary to psychologic factors. A dietary history disclosed that the patient usually ate no breakfast and at other meals ate mostly polished rice with very little meat and/or vegetables. In addition, when he became ill, he ate only a broth of rice and water.

We administered intravenous fluids calculated to provide maintenance requirements and to correct a fluid deficit of approximately 10%. Despite rehydration, the patient's condition continued to deteriorate slowly.

By the seventh hospital day, abdominal pain, dyspnea, and oliguria developed. The following physiologic measures were obtained: blood pressure, 70/30 mm Hg; heart rate, 120 beats per minute; respirations, 40/min; and oral temperature, 35.5°C. The patient was anxious and had marked edema of the face, neck, and upper extremities. He had bilateral rales in the lower posterior lung fields, a pounding thrill on palpation, and a fixed split S_2, and increased P_2, as well as a grade 2/6 systolic ejection murmur at the lower left sternal border. Peripheral pulses were bounding. The liver was enlarged and pulsating. Deep tendon reflexes were absent.

The patient was hyponatremic (sodium, 130 mmol/L), had a metabolic lactic acidosis (HCO_3, 10 mmol/L; lactate, 3.4 mmol/L) with deteriorating renal function (serum urea nitrogen, 25.3 mmol/L; creatinine, 160 μmol/L). Substantial liver dysfunction was present with an aspartate aminotransferase level of 79 U/L and a total bilirubin plasma concentration of 94 μmol/L. He had roentgenographic evidence of cardiomegaly, pulmonary edema, and a left-sided pleural effusion. He had a right-sided bundle branch block and left axis deviation. Right atrial and ventricular enlargement with 1+ tricuspid regurgitation was demonstrated on echocardiographic examination. Ultrasound examination showed the kidneys to be normal, with no ureteral obstruction. Renal blood flow was normal with diffuse parenchymal dysfunction

Hemodynamic Monitoring Over a 36-Hour Period							
	Day 8			Day 9			Day 10,
Hemodynamic Measure	6 PM	8 PM*	10 PM	2 AM	8 AM	10 PM	6 AM
Heart rate, beats/min	100	100	100	98	80	76	54
Pressure, mm Hg							
R atrium	8	8	7	9	9	10	14
Pulmonary artery systolic	68	70	58	53	47	40	24
Pulmonary artery end-diastolic	30	30	25	28	25	19	16
Pulmonary-capillary wedge	14	13	12	15	14	14	14
Cardiac index, L/min/m²	7.8	...	...	...	6.5	5.9	4.4
Systemic vascular resistance, dyne•s/cm⁵	484	...	...	...	440	566	1008

*Thiamine administered.

visible on angiographic study. The Table documents the hemodynamic measurements. The pulmonary artery pressure was elevated to 68/30 mm Hg (normal, 25/8 mm Hg); the right atrial pressure was normal at 8 mm Hg; and pulmonary capillary wedge pressure was 14 mm Hg (normal, 4 to 12 mm Hg). Cardiac output was high at 12.0 L/min, with a cardiac index of 7.8 L/min/m² (normal, 2.5 to 3.6 L/min/m²) and a low systemic vascular resistance of 484 dyne·s/cm⁵.

There was no evidence of sepsis, hepatorenal syndrome, atrioventricular shunt, Paget's disease, severe anemia, or thyrotoxicosis, and a diagnosis of beriberi was considered. We were unable to measure the standard red blood cell transketolase assay, and a trial of thiamine therapy with 100 mg given intravenously was initiated on the eighth hospital day. Low doses of dopamine and furosemide were administered as permitted with hemodynamic monitoring. As is evident from the Table, 34 hours after the administration of thiamine, the right-sided pulmonary artery pressure and the cardiac index were dramatically decreased (to 24/16 mm Hg and 4.4 L/min/m², respectively) and the systemic vascular resistance had returned to normal (1008 dyne·s/cm⁵). A similar resolution was noted for the metabolic acidosis and other metabolic abnormalities, including abnormal renal and liver functions. The electrocardiogram remained unchanged, but the echocardiographic findings became normal. The cardiomegaly and pulmonary edema resolved.

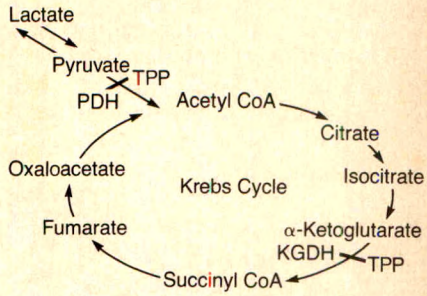
Comment.—Beriberi was first described by Oriental physicians in the *Niching* and is Singhalese for "weakness."[1] In 1929, Aasmeer and Wenkeback depicted beriberi as right-sided hyperkinetic failure, with wide pulse pressures, flushed skin, and rapid circulation.[2] The Japanese noted two distinct clinical presentations. A "wet" form with the gradual onset of massive dependent edema was often fulminant and terminated in vascular collapse and death, and was named *shoshin beriberi* (*sho* is Japanese for acute damage, *shin* means heart). A "dry" form was associated with weakness and peripheral neuropathy.

Beriberi is most common today in alcoholics and persons eating polished rice. The clinical constellation of hypotension, cardiac failure, lactic acidosis, and oliguria is common. Thiamine deficiency results either from decreased intake of thiamine-rich foods such as legumes, meats, and rice polishings, from the intake of thiaminases from sources such as betel nut, or chewed tea leaves.[3] A recent report documented the reemergence of beriberi among Japanese adolescents whose diets consisted predominantly of polished rice and a high carbohydrate content.[4] The dietary history of our patient is similar to that reported for these Japanese youths.

The key to understanding the pathophysiology of beriberi is to review the major functions of thiamine as the coenzyme thiamine pyrophosphate (TPP) in human physiology. The Figure is a schematic diagram of the Krebs cycle and the role of TPP in carbohydrate metabolism. Thiamine pyrophosphate first acts as a coenzyme to pyruvate dehydrogenase as it converts pyruvate to acetyl coenzyme A. Blocking this reaction leads to the buildup of pyruvate and its conversion to lactate, leading to metabolic lactic acidosis.

Second, TPP is a coenzyme to α-ketoglutarate dehydrogenase, which converts α-ketoglutarate into succinyl coenzyme A. Blocking this step leads to decreased availability of energy from adenosine triphosphate. This preferentially affects tissues with a high energy consumption, such as cardiac muscle, resulting in cardiac dysfunction.

Thiamine pyrophosphate is also a coenzyme for transketolase, which converts ribose-5-phosphate to sedoheptulose-7-phosphate in the hexomonophosphate shunt. The measurement of this transketolase activity in red blood cells is the current standard for measurement of thiamine deficiency. Additionally, a TPP effect is often used as a measurement by adding thiamine to red blood cells and measuring the increase in transketolase activity.



Role of thiamine in carbohydrate metabolism. Thiamine pyrophosphate (TPP) is coenzyme for pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH) within Krebs tricarboxylic acid cycle. Thiamine deficiency results in increased production of lactate and decreased energy availability. CoA indicates coenzyme A.

Diagnosis in the clinical setting is often difficult. Urinary and serum thiamine levels have been shown to correlate poorly with tissue levels.[5] Red blood cell levels of transketolase and the TPP effect correlate closely with tissue levels of thiamine.[6] However, these tests are not commonly available. Blood must be drawn in a lithium-heparin tube and the specimen must be frozen immediately, or the results may be invalid. The clinical constellation of hypotension, high output cardiac failure, low systemic vascular resistance, lactic acidosis, and oliguria should arouse clinical suspicion of beriberi. Administration of 100 mg of thiamine intravenously will lead to the resolution of symptoms long before laboratory results are available.

In our patient, all of the classic symptoms of shock, heart failure, lactic acidosis, and oliguria were present. In addition, hepatic dysfunction with jaundice added to the confusion in diagnosing this uncommon disease. An intern consulted her handbook on differential diagnosis and recommended the treatment with thiamine, thereby saving this 17-year-old patient's life. Physicians need to consider nutritional deficiency in all of our patients, but particularly in those

with appropriate nutritional histories and compatible symptoms.

KAREN VRCHOTA, MD
Department of Family Practice
CHARLES N. OBERG, MD
Department of Pediatrics
Hennepin County Medical Center
701 Park Ave South
Minneapolis, MN 55415
KEVIN N. HARRIS, MD
Department of Internal Medicine
Dartmouth Hitchcock
Medical Center
2 Maynard St
Hanover, NH 03756

1. Wolf PL, Levin MB: Shoshin beriberi. *N Engl J Med* 1960;262:1302-1306.
2. Wagner PL: Beriberi heart disease. *Am Heart J* 1965;69:200-205.
3. Vimokesant S, Kunjara S, Rungruangsak K, et al: Beriberi caused by antithiamine factors in food and its prevention. *Ann NY Acad Sci* 1982;378:123-136.
4. Kawai H, Wakabayashi K, Matsumura, A, et al: Reappearance of beriberi heart disease in Japan. *Am J Med* 1980;62:383-386.
5. Akbarian M, Yankopoulos NA, Abelmann WH: Hemodynamic studies in beriberi heart disease. *Am J Med* 1966;41:197-212.
6. Akbarian M, Dreyfus PM: Blood transketolase activity in beriberi heart disease. *JAMA* 1968;203:77-80.

Injury Prevention: Drowning

Sir.—At the end of her editorial in the June 1988 issue of *AJDC*, Dr Noyes[1] recommends the formation of several national coalitions to attack the most commonly encountered injuries to children. One of her suggestions is to form a Child Pool Safety Group composed of "health care workers along with swimming pool manufacturers, YMCAs, YWCAs, and others." Such a group is already in existence. Encumbered with an awkward title, the National Swimming Pool Safety Committee has been in existence since 1985. It was organized by the Consumer Product Safety Commission (CPSC) and the National Spa and Pool Institute, the swimming pool industry's trade organization. Specific injuries targeted were childhood drownings and diving accidents. Membership on the various working committees has included representatives of the YMCA, the American Red Cross, and the National Safety Council, as well as attorneys, consumer advocates, educators, and physicians.

As part of their work, the CPSC identified childhood drownings as a priority issue for the past three fiscal years. The commission recently published the results of a large epidemiological study completed in 1986, which confirms many of the commonly held beliefs about childhood swimming pool drownings and provides new insights into prevention strategies.

Multiple educational materials have been developed by and distributed through the committee. Most recently, a poster and copies of a brochure titled "Children Aren't Waterproof" were sent to 10 000 pediatricians around the country for use in their offices. In addition, a packet of ready-made press releases intended for use by local groups and endorsed by former President Reagan has been distributed nationally for the past two years through Operation Water Watch. In many areas of the country, drowning prevention groups have "come of age." Communication between these groups has been facilitated by regional conferences sponsored by the CPSC. Much work remains to be done, including further education of pediatricians and local members of the pool industry, development of standards for pool safety covers and fencing hardware, and research on the effectiveness of current educational, technical, and legislative solutions.

Information on the committee's activities and available publications can be obtained by contacting the Consumer Affairs Office of the CPSC, Washington, DC.

BARBARA SMITH, MD
Information and Education
Subcommittee
National Swimming Pool
Safety Committee
6565 E Carondelet
Tucson, AZ 85710

1. Noyes D: Trauma and toxins. *AJDC* 1988; 142:593-594.

In Reply.—I am grateful to Dr Smith for taking the time and trouble to write *AJDC* about the National Swimming Pool Safety Committee. My unfamiliarity with this joint effort of the Consumer Product Safety Commission and the National Spa and Pool Institute may be attributable to the "awkward title" of the organization to which Dr Smith refers. It may also be due in part to the lack of publicity that has attended the efforts of this group.

At any rate, I shall look forward to learning more about the activities of the group. And perhaps, in some small way, I can help spread the good news.

DOROTHY NOYES, MPH, PHD
225 E 73rd St
Apt 11A
New York, NY 10021

Bone Mineral Status in Hypopituitarism

Sir.—We read with interest the article by Witz et al[1] in the August 1988 issue of *AJDC* regarding growth disturbance in hypopituitarism and would like to add our observations on bone mineral status in patients with hypopituitarism.

The bone mineral status of nine male patients with hypopituitarism (due to various causes) was analyzed by single-photon absorptiometry at the nondominant distal radius. The patients were 14 to 21 years old (mean age, 18 years); the pubertal stage was Tanner I to II. Hand radiography showed that the epiphyses were open, and serum testosterone levels were below 4 nmol/L in the presence of low serum gonadotropin levels. All patients had received levothyroxine sodium and synthesized human growth hormone, three had received hydrocortisone (5 to 15 mg/d), and none had received sex steroid hormone replacement therapy.

In five of the nine patients, the radial bone mineral content (in grams per square centimeter) was at least 2.0 SDs below the mean value that corresponds to chronological age. Even in the remaining four patients, the bone mineral content was 1 SD below normal. Especially in the two patients aged 14 and 18 years receiving hydrocortisone replacement therapy, the bone mineral content was revealed to be remarkably osteopenic (0.42 and 0.41 g/cm^2, respectively).

Abundant evidence links decreased bone mass with estrogen-deficient status in women, such as occurs after menopause, surgical oophorectomy, or premature ovarian failure.[2] In contrast to estrogen deficiency, the prevalence and pathogenesis of osteopenia in hypogonadism in male patients is not fully known, although gonadal function seems to be important for maintaining a normal mineral content.[3,4] A recent study, however, has demonstrated that osteopenia in hypogonadal men is alleviated after normalization of the sex hormone concentration.[5]

During normal puberty, a marked increase in bone density occurs, which is thought to be due to a rise in sex steroid secretion.[6,7] In this period, increases in the serum levels of alkaline phosphatase and osteocalcin (both of which are markers of osteoblastic activity) have been noted.[8] Androgen

deficiency during puberty seems to be a risk factor for osteopenia in adolescent boys and young male adults. Since skeletal mass in adulthood is the result of both the amount of bone gained during growth and its subsequent rate of loss, it seems that the factors affecting bone density during growth are important determinants of future skeletal resistance to fracture.[3,9]

Our patients with hypopituitarism were all hypogonadal (low serum testosterone level) due to reduced gonadotropin release (hypogonadotropic hypogonadism). Therefore, the decreased bone mineral content (osteopenia) in hypopituitarism associated with hypogonadotropic hypogonadism could be caused by inadequate bone mineralization during puberty. In addition, in such patients receiving hydrocortisone replacement, corticosteroid excess is also a risk factor for osteopenia.[10] Institution of sex steroid hormone (testosterone) replacement therapy at an appropriate age in male patients with hypopituitarism would not only facilitate a more efficient growth hormone effect[1] but would also stimulate the pubertal increase in bone mineral content.

Osamu Arisaka, MD
Madoka Arisaka, MD
Atsuto Hosaka, MD
Keijiro Yabuta, MD
Department of Pediatrics
Juntendo University School of Medicine
2-1-1 Hongo, Bunkyo-ku
Tokyo 113, Japan

1. Witz L, Josefsberg Z, Kaufman H, et al: When should hydrocortisone therapy be instituted in children with hypopituitarism? *AJDC* 1988;142:881-883.
2. Johnston CC Jr, Hui SL, Witt RM, et al: Early menopausal changes in bone mass and sex steroids. *J Clin Endocrinol Metab* 1985;61:905-911.
3. Finkelstein JS, Klibanski A, Neer RM, et al: Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. *Ann Intern Med* 1987;106:354-361.
4. Arisaka O, Hoasaka A, Arisaka M, et al: Testosterone and bone density in hypogonadism. *Eur J Pediatr*, in press.
5. Finkelstein JS, Klibanski A, Neer M, et al: Increases in bone density during treatment of men with idiopathic hypogonadotropic hypogonadism, abstracted. *Clin Res* 1988;36:384.
6. Chesney RW, Shore RM: The noninvasive determination of mineral content by photon absorptiometry. *AJDC* 1982;136:578-580.
7. Krabbe S, Hummer L, Christiansen C: Longitudinal study of calcium metabolism in male puberty: II. Relationship between mineralization and serum testosterone. *Acta Paediatr Scand* 1984;73:750-755.
8. Johansen JS, Giwercman A, Hartwell D, et al: Serum Gla-protein as a marker of bone growth in children and adolescents: Correlation with age, height, serum insulin-like growth factor I and serum testosterone. *J Clin Endocrinol Metab* 1988;67:273-278.
9. Gilsanz V, Gibbens DT, Roe TF, et al: Vertebral bone density in children: Effect of puberty. *Radiology* 1988;166:847-850.
10. Hyams JS, Carey D: Corticosteroids and growth. *J Pediatr* 1988;113:249-254.

Occult Bacteremia in Children With Simple Febrile Seizures

Sir:—The association of bacteremia and febrile seizures described by Chamberlain and Gorman[1] in a recent *AJDC* article has been recognized at least since 1967, when two of three patients with pneumococcal bacteremia described by Belsey[2] presented with seizures. Five of 11 children with occult pneumococcal bacteremia described in 1970[3] presented with seizures, and all had sterile cerebrospinal fluid. As Chamberlain and Gorman point out, obtaining blood cultures should always be considered for children with febrile seizures.

We should recall that children with pneumococcal bacteremia, with or without seizures, who have sterile cerebrospinal fluid initially may go on to develop meningitis, while receiving oral or even parenteral antibiotics.[2]

Daniel E. Torphy, MD
Department of Pediatrics
Medical College of Wisconsin
1700 W Wells St
Milwaukee, WI 53233

1. Chamberlain JM, Gorman RL: Occult bacteremia in children with simple febrile seizures. *AJDC* 1988;142:1073-1076.
2. Belsey MA: Pneumococcal bacteremia. *AJDC* 1967;113:588-589.
3. Torphy DE, Ray CG: Occult pneumococcal bacteremia. *AJDC* 1970;119:336-338.

Sir:—The recent article by Chamberlain and Gorman in *AJDC* examined the incidence of bacteremia in children with simple febrile convulsions. Of note was that all five instances of bacteremia documented were caused by *Streptococcus pneumoniae*. Similarly, Hamrick and Murphy[1] found a high rate (80%) of *S pneumoniae* isolated in bacteremic children who experienced febrile convulsions, and McIntyre et al[2] found that a high percentage of children with *S pneumoniae* occult bacteremia experienced seizures with fever.

I surveyed the results of blood cultures performed on children evaluated from 1985 to 1988 in the Emergency Department of Children's Hospital of Wisconsin, Milwaukee, for febrile convulsions. During this time, there were 17 instances of bacteremia in those children who fulfilled criteria for simple febrile convulsions (patient age between 6 months and 5 years, generalized seizure activity of <15 minutes duration, presence of high fever [>39°C], and no underlying neurologic disorder identified [including central nervous system infection]). The age distribution was three patients under 12 months, eight patients 12 to 24 months, four patients 24 to 36 months, and two patients older than 36 months. There were eight patients with a temperature of 39°C to 40°C, and nine patients with a temperature greater than 40°C. Overall, 15 (88%) of 17 children had *S pneumoniae* isolated; the other two cases were caused by *Haemophilus influenzae*. The clinical features and outcomes were similar in those patients with bacteremia because of the respective organisms.

As compared with previously described distributions of pathogenic organisms responsible for childhood bacteremia,[3,4] my results show a more skewed distribution of the organisms responsible for bacteremia in children with simple febrile convulsions. Several theoretical explanations may account, in part, for the disproportionately high rate of isolation of *S pneumoniae* in children who experience febrile convulsions with bacteremia.

1. It is theorized that febrile convulsions are induced by a rapid rate of temperature elevation in the young child.[5] Previous studies have noted that pneumococcal bacteremia is commonly associated with the acute onset of spiking-patterned high fevers[6]; in one large series, approximately 50% of the patients with *S pneumoniae* bacteremia presented with a temperature greater than 40°C.[7] It may be that the characteristic acute-onset spiking fever that predisposes to febrile convulsions is more often associated with bacteremia caused by this organism, compared with other common causes of bacteremia.

2. It is possible that *S pneumoniae*, like the bacterium *Shigella*, produces an as yet undefined neurotoxin that potentiates the propensity for convulsive activity.

3. An inherent sampling bias may exist when comparing the two most common organisms associated with bacteremia in children with simple febrile convulsions. As compared with pneumococcemia, *H influenzae* bac-

teremia is highly associated with concomitant soft-tissue infections, including meningitis. Since those patients with meningitis would not fulfill the criteria for defining simple febrile convulsions, relatively more children with *H influenzae* bacteremia would be eliminated from consideration.

Physicians should be aware that bacteremia in children who experience simple febrile convulsions is usually due to *S pneumoniae*. Empiric antibiotic therapy initiated in this clinical situation should be directed toward this pathogen.

WILLIAM A. BONADIO, MD
Department of Pediatrics
Children's Hospital of Wisconsin
1700 W Wisconsin Ave
Milwaukee, WI 53233

1. Hamrick HJ, Murphy TF: Bacteremia in 28 ambulatory children: Relationship to pneumonitis and meningitis. *Clin Pediatr* 1978;17:109-112.

2. McIntyre P, Kennedy R, Harris F: Occult pneumococcal bacteremia and febrile convulsions. *Br Med J* 1983;286:203-206.

3. McGowan JE, Bratton L, Klein JO, et al: Bacteremia in febrile children seen in a 'walk-in' pediatric clinic. *N Engl J Med* 1973;288:1309-1312.

4. McCarthy PL, Grundy GW, Spiesel SZ, et al: Bacteremia in children: An outpatient clinical review. *Pediatrics* 1976;57:861-868.

5. Wegman M: Factors influencing relation of convulsions and hyperthermia. *J Pediatr* 1939; 14:190-202.

6. Heldrich FJ: *Diplococcus pneumoniae* bacteremia. *AJDC* 1970;119:12-18.

7. Burke JP, Klein JO, Gezon HM, et al: Pneumococcal bacteremia: Review of 111 cases. *AJDC* 1971;121:353-359.

In Reply.—We thank Drs Torphy and Bonadio for their comments. These clinicians present data to answer a different question from that which we attempted to answer in our study. We determined the rate of occult bacteremia in children with simple febrile seizures, whereas Drs Torphy and Bonadio report occurrences of simple febrile seizures in children with bacteremia.

Dr Torphy notes that bacteremia has been associated with simple febrile seizures since 1967. Our study grew out of the desire to determine the rate of occult bacteremia in these patients.

Dr Bonadio raises an interesting question. Is there something unique about bacteremia caused by *S pneumoniae* that makes a patient more likely to experience a febrile convulsion? To answer this question directly, one would need to compare the rate of febrile seizures in a group with pneumococcal bacteremia with the rate of a similar group with other types of bacteremia. To our knowledge, this has not been done.

Dr Bonadio has chosen to look at this question from a slightly different perspective, using the positive blood culture as an entry criterion and febrile convulsion as an outcome. Comparing his group of 17 patients with bacteremia and febrile seizures with historical control subjects with bacteremia alone drawn from the literature, he noted a higher rate of pneumococcal bacteremia in his patients with simple febrile seizures. Fifteen of 17 patients had pneumococcal bacteremia; two had bacteremia caused by *H influenzae*.

Is this ratio of *S pneumoniae* to *H influenzae* higher than that previously reported? Dr Bonadio cites the work of McGowan et al, in which 19 patients had pneumococcal disease and six had *H influenzae* type b (HIb). When one excludes those with pneumonia, the data compiled by McGowan et al (with 14 patients with pneumococcus and two with HIb) become nearly identical to Dr Bonadio's.

The thrust of our study of patients with simple febrile seizures was to identify bacteremia in patients who had no focus of infection (except otitis media), and who appeared well enough to be discharged from the emergency department. This is consistent with the evolution of the concept of occult bacteremia. Early reports included bacteremia with or without foci of infection, whereas later authors included only those patients without focal infections other than an upper respiratory tract infection or otitis media.

Reviewing articles on bacteremia, we present the proportions of *S pneumoniae* to *H influenzae* that others have found in patients without focal infections other than otitis media (Table). The pneumococcus to HIb ratio has been 9:1 (120:13) in patients with occult bacteremia. In summary, historical data in patients without febrile seizures have a proportion of pneumococcal disease similar to Dr Bonadio's.

Proportion of Patients With *Streptococcus pneumoniae* vs *Haemophilus influenzae**

Source, y	URI/FUO	Otitis Media	Pneumonia	Other	Total Occult
McGowan et al, 1973	...	...	5:4	...	14:2
Teele et al,[1] 1975	4:1	2:0	8:0	1:1	6:1
McCarthy et al, 1976	14:2	13:1	4:3	9:35	27:3
McCarthy et al,[2] 1977	...	...	...	...	15:2
Hamrick and Murphy, 1978	5:1	8:5	4:2	...	13:1†
Jaffe et al,[3] 1987	36:3	...	...	...	36:3
Carroll et al,[4] 1983	9:1	...	...	...	9:1
Total	...	...	...	...	**120:13**

*URI indicates upper respiratory tract infection; FUO, fever of undetermined origin. Values are number of patients with *S pneumoniae*: number of patients with *H influenzae*.
†Five patients with *H influenzae* type b and otitis media "appeared seriously ill."

We agree with Dr Bonadio that empiric antibiotic therapy, when indicated, should be for a broad spectrum but directed primarily against pneumococcus. In Dr Bonadio's data, 35% (6/17) of his bacteremic patients were older than 2 years of age. We reported 40% (2/5) in this age group. As primary care physicians, it is useful to be reminded that bacteremia occurs in older children.

JAMES M. CHAMBERLAIN, MD
Trauma Center
Children's Hospital
National Medical Center
111 Michigan Ave NW
Washington, DC 20010
RICHARD L. GORMAN, MD
Maryland Poison Center and
St Agnes Hospital
20 N Pine St
Baltimore, MD 21201

1. Teele DW, Pelton SI, Myles JAG, et al: Bacteremia in febrile children under 2 years of age: Results of cultures of 600 consecutive febrile children seen in a 'walk-in' clinic. *J Pediatr* 1975; 87:227-230.

2. McCarthy PL, Jekel JF, Dolan TF: Temperature greater than or equal to 40°C in children less than 24 months of age: A prospective study. *Pediatrics* 1977;59:663-668.

3. Jaffe DM, Tanz RR, Davis AP, et al: Antibiotic administration to treat possible occult bacteremia in febrile children. *N Engl J Med* 1987; 317:1175-1180.

4. Carroll WL, Farrell MK, Singer JI, et al: Treatment of occult bacteremia: A prospective randomized clinical trial. *Pediatrics* 1983;72:608-612.

Who has time for allergies when you are performing emergency surgery

Kids can't operate when allergy symptoms get in their way. Tavist® Syrup (clemastine fumarate) 0.67mg/5ml, helps kids by effectively relieving symptoms of allergic rhinitis and mild urticaria.

With a pleasant citrus flavor and convenient b.i.d. dosage, Tavist® Syrup provides up to 12 hours of relief.

Prescribe Tavist® Syrup. So kids can perform to their full potential.

Tavist® Syrup. Lets kids be kids 12 hours long

(clemastine fumarate) 0.67mg/5ml

© 1989 Sandoz Pharmaceuticals Corporation

Please see a brief summary of prescribing information on the following page.

TAS-189-1

BRIEF SUMMARY

TAVIST®

(clemastine fumarate) SYRUP 0.5 mg/5 ml
(present as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

Tavist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see *DOSAGE AND ADMINISTRATION*).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see *PRECAUTIONS — Drug Interactions* in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see *PRECAUTIONS — Nursing Mothers* in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist® (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (6 mg clemastine).

For Urticaria and Angioedema — The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED

Tavist® (clemastine fumarate) Syrup

Clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

[TAS-Z3 APRIL 1, 1986]

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

INDEX TO ADVERTISERS

Abbott Laboratories 297-298
Allen & Hanburys, Division of Glaxo, Inc. 324A-B, 372A-D, 373
American Academy of Pediatrics 351

Burroughs Wellcome Company 277-278

Carnation Company 268A-H, 352
Cejka & Company 298
Connaught Laboratories, Inc. 322-324

Fisons Corporation 266, 383
Forest Pharmaceuticals, Inc. 279

ICN Pharmaceuticals, Inc. 276A-D

Lederle Laboratories 267-268

McNeil Consumer Products Company 300
Mead Johnson Nutritional Division ..... Cover 2

National Biological Corporation 278
National Institutes of Health 278

Osler Institute 384

Praxis Biologics 332A-D

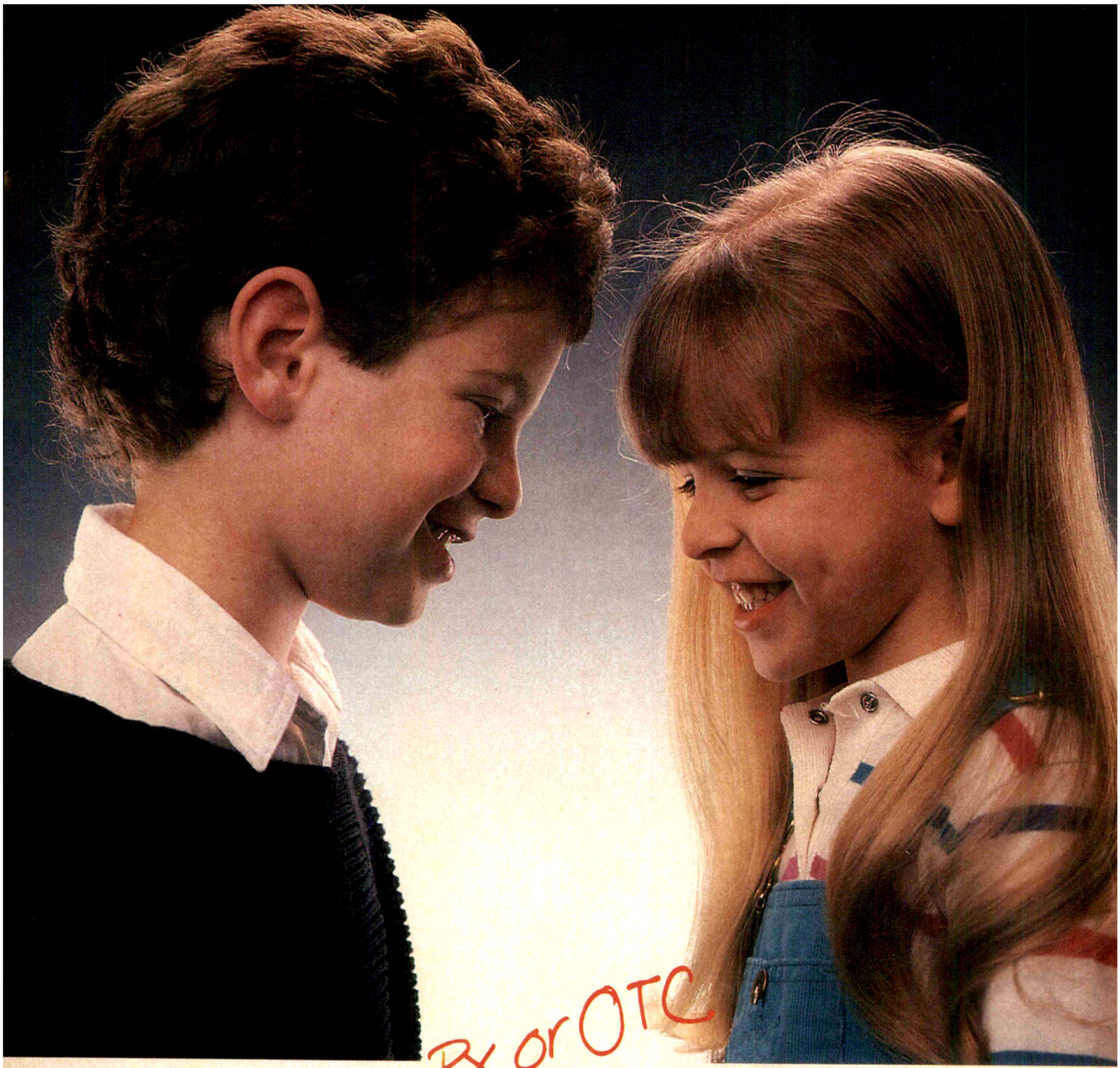
A.H. Robins Company 378
Rorer Pharmaceuticals 295-296
Ross Laboratories 280

Sandoz Pharmaceuticals ..... 262, 275-276, 283, Cover 3
E.R. Squibb & Sons, Inc. 284-286

University of Alabama 298

Wyeth-Ayerst Laboratories ..... 264, Cover 4

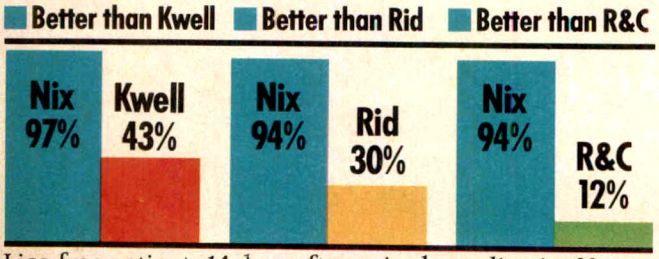
While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.



The best treatment to kill lice and nits

97% effective with one application

Clinical studies prove Nix™ kills lice and nits and protects against reinfestation better than Rid,® Kwell,® or R&C Shampoo.® Only Nix provides 14-day protection against reinfestation–*with one application*–and no evidence of CNS toxicity as reported with lindane overexposure.[1]



Lice-free patients 14 days after a single application.[2,3]
(Rid labelling requires a second application at 7-10 days.)

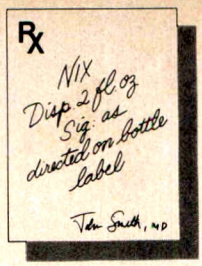
Nix FOR LICE®
CREME RINSE
permethrin 1%

Call 1-800-FOR-LICE
to report head lice outbreaks

Copr. ©1988 Burroughs Wellcome Co. All rights reserved. NI-122
Please see adjacent page for brief summary of prescribing information.

Wellcome

Nix® FOR LICE
CREME RINSE
permethrin 1%



PEDICULICIDAL/OVICIDAL ACTIVITIES: *In vitro* data indicate that permethrin has pediculicidal and ovicidal activity against *Pediculus humanus* var. *capitis*. The high cure rate (97-99%) of Nix in patients with head lice demonstrated at 14 days following a single application is attributable to a combination of its pediculicidal and ovicidal activities and its residual persistence on the hair which may also prevent reinfestation.

INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus* var. *capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should consult their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing.

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually a consequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp. Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for cosmetic or other reasons.

SHAKE WELL BEFORE USING.

HOW SUPPLIED: Nix (Permethrin) 1% (wt./wt.) Creme Rinse is supplied in plastic squeeze bottles that contain 2 fl. oz. weighing 56 g. (NDC-0081-0780-81)

Store at 15°-25°C (59°-77°F).

1. Davies J, Dedhia H, Morgade C, et al: Lindane poisonings, *Arch Dermatol* 1983;119:142-144.
2. Taplin D, Meinking T, Castillero P, et al: Permethrin 1% creme rinse for the treatment of *pediculus humanus* var *capitis* infestation. *Pediatr Dermatol* 1986;3:344-348.
3. Taplin D, Meinking T: Pyrethrins and pyrethroids for the treatment of scabies and pediculosis. *Semin Dermatol* 1987;6:125-135.

Burroughs Wellcome Co.
3030 Cornwallis Road
Wellcome Research Triangle Park, NC 27709

CONGENITAL ADRENAL HYPERPLASIA REFERRAL

The Clinical Center requests the cooperation of physicians in the referral of growing children with congenital adrenal hyperplasia for a study on the relative effectiveness of once-daily compared to twice-daily hydrocortisone administration. The bone age must be ≤ 11 years for boys and ≤ 9 years for girls.

Patients will be followed in conjunction with their referring physicians over the 2-year duration of the study. At the completion of the study patients will be returned to the care of their referring physician. Please write or telephone:

Dr. Louisa Laue or
Dr. Gordon B. Cutler, Jr.
Building 10, Room 10N-262
National Institutes of Health
Bethesda, Maryland 20892
Tel: (301) 496-4686

STREP TEST™
SHEEP BLOOD AGAR PLATES
LABORATORY CULTURE MATERIALS

- BACITRACIN DISKS
- URI-DIP® URINE CULTURE MATERIALS
- DELUXE INCUBATORS
- DISPENSERS
- INNOCULATING LOOPS
- SWABS

AVAILABLE FROM:
UNIVERSAL BIOLOGICAL LABS
DIAGNOSTIC DIVISION OF:
NATIONAL BIOLOGICAL CORPORATION

1532 ENTERPRISE PARKWAY
TWINSBURG, OHIO 44087
(216) 425-8180
OUTSIDE OHIO: 1-800-338-5045
IN OHIO: 1-800-227-6294

ORDER TODAY
FOR IMMEDIATE DELIVERY

Re-introduce The Oldest Advance In Medicines.

It's called talking. If your older patients don't ask you about the prescriptions they've been given, make it a point to tell them what they need to know. Make sure they know the medicine's name, how and when to take it, precautions, and possible side effects. Encourage them to write down the information and ask you questions about things they don't understand.

You'll also want to take a complete medications history including both prescription *and* non-prescription medicines. The history can alert you to the potential for drug interactions and help you simplify their regimen.

Re-introduce the oldest advance in medicines. Make talking a crucial part of your practice. Because good, clear communication about medicines isn't a thing of the past. It's the way to a healthier future.

Before they take it, talk about it.

National Council on
Patient Information and Education.
666 Eleventh St. N.W. Suite 810
Washington, D.C. 20001

Now, MDI therapy is available to more patients than ever before

New AeroChamber®
WITH *MASK* (aerosol holding chamber)

Permits easier metered-dose-inhaler (MDI) therapy in children and the elderly (see boxed statement below). The device consists of an aerosol holding chamber with a soft, flexible mask that covers the patient's nose and mouth. A one-way valve holds the medication until the patient inhales. Expired air is vented through exhalation ports. AeroChamber with *Mask* is economical and fits virtually any inhaler.

IMPORTANT INFORMATION
Package insert dosing instructions should be consulted for all metered dose inhalers (MDIs) when used with AeroChamber with *Mask*.

Dosage and administration recommendations vary for different MDIs, and the limitations and conditions of use for each product should be considered before utilizing this device, particularly for younger and older patients.

☐ **Yes, I am interested in the New AeroChamber® with *Mask*. Please send more information.**

☐ **Enclosed is my check or money order for:**

#Units		Price		Total
_____	×	**$22.00**	=	_____

Minimum order—6 units. Price includes postage and handling.

Name _____
(please print)
Address _____
City _____
State _____ Zip _____
Phone ( ) _____

Clip and mail to: **AeroChamber® with *Mask***
FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

For more information or to place an order now, call 1-800-325-1605.

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63043-9979

© 1988 Forest Pharmaceuticals, Inc.

AWM-008-88

From Ross Laboratories!

ALIMENTUM™

Protein Hydrolysate Formula With Iron

For the dietary management of infants with protein sensitivity, carbohydrate malabsorption, and fat malabsorption.

The only ready-to-feed casein hydrolysate infant formula that combines convenience with formulation advantages to meet all your hydrolysate feeding needs.

- A caloric distribution similar to that of breast milk.
- An extensively hydrolyzed infant formula with proven hypoallergenicity.
- A dual source of carbohydrate at an appropriate level to minimize the risk of carbohydrate intolerance.
- Fifty percent of the fat from medium-chain triglycerides — an easily digested and absorbed fat source.

Meeting All Your Hydrolysate Feeding Needs

© 1988 Ross Laboratories

ROSS LABORATORIES
COLUMBUS, OHIO 43216
Division of Abbott Laboratories, USA

B101/8890

Adult Immunization: Knowledge, Attitudes, and Practices—DeKalb and Fulton Counties, Georgia, 1988

VACCINE-PREVENTABLE diseases are a major problem in adults.[1] In particular, influenza and pneumococcal disease account for approximately 60,000 deaths each year among persons greater than or equal to 65 years of age. Many of these deaths could be prevented through appropriate vaccination, but most adults are not immunized.[1]

In July 1988, the DeKalb County Board of Health, Fulton County Health Department, Georgia Department of Human Resources, and CDC surveyed persons greater than or equal to 65 years of age who lived in DeKalb and Fulton counties, Georgia. This survey assessed knowledge, attitudes, and practices regarding influenza and pneumococcal immunizations. Interviews were conducted by telephone or in person using the same questionnaire[1] DeKalb and Fulton counties, respectively, 13 and 50 housing communities for older adults who lived independently were identified. Seven communities (five in DeKalb County and two in Fulton County) participated in the in-person interviews. For all the remaining communities in DeKalb County and half of those remaining in Fulton County, telephone numbers for interviews were selected from a reverse telephone directory. On a Wednesday evening, telephone calls were made to every other residence. The following day, interviewers conducted voluntary personal interviews of residents passing through lobbies of the housing in the seven previously identified communities.

The data were combined for this report because the same questionnaire was used for the telephone and in-person surveys in both counties, county-specific results were similar, and results from telephone and in-person interviews were similar.

A total of 867 interviews were completed—486 (26%) of 1851 telephone numbers called, 380 (26%) in-person interviews of the estimated 1452 residents, and one of unknown type. Because influenza and pneumococcal vaccines are recommended for all persons aged greater than or equal to 65 years,[2-5] this analysis is restricted to responses from the 716 (83%) residents who were in this age group and who identified their county of residence as DeKalb County (354 (49%)) or Fulton County (362 (51%)). Of these persons, 609 (85%) were female, 594 (83%) were white, and 122 (17%) were black. The median age was 78 years. For comparison, county-specific demographic data are shown in Table 1.

Six hundred forty-two (90%) of the respondents reported that they were aware of influenza vaccine. Of these, 355 (55%) reported receiving it within the past year. Fifty-nine percent of white respondents and 37% of black respondents reported receiving influenza vaccine in the past year (Table 2) (prevalence ratio (PR) = 1.6, 95% confidence interval (CI) 1.3, 2.0). No difference was found in vaccination status by sex.

Of factors that might be associated with influenza vaccination status, including race and gender, the most important was a recommendation for vaccination by a healthcare provider. Seventy-five percent (447) of the 596 respondents who were aware of influenza vaccine and responded to the question reported that their healthcare provider had recommended influenza vaccination. Seventy-five percent of persons to whom immunization had been recommended reported being vaccinated within the last year, compared with 7% of those who had not had a recommendation (Table 2) (PR = 11.2; 95% CI 8.1, 15.5). This association of recommendation and vaccination was present for both races.

Of the 642 respondents who were aware of the influenza vaccine, 466 (73%) reported negative attitudes toward it (i.e., that influenza vaccine itself causes illness, does not protect against influenza, or is unnecessary). Fifty percent of those with a negative attitude who responded to the question reported being vaccinated within the last year. Seventy percent of respondents with positive attitudes reported being vaccinated (PR = 0.7, 95% CI 0.6, 0.8). Of respondents with negative attitudes whose health-care provider had or had not recommended vaccination, 70% and 7%, respectively, had been vaccinated (Table 2) (PR = 10.8, 95% CI 7.3, 16.0). Of respondents with positive attitudes whose health-care provider had or had not recommended immunization, 87% and 8%, respectively, had been vaccinated (PR = 11.3, 95% CI 6.3, 20.3).

Three hundred eighty-one (53%) of respondents were aware of a vaccine to prevent pneumococcal disease, and 146 (38%) of these reported having received it. There was no association between race or gender and pneumococcal vaccination status.

The most important factor associated with pneumococcal vaccination status, as with influenza vaccination status, was vaccine recommendation by a health-care provider. Of persons who were aware of the pneumococcal vaccine and responded to the question, 169 (53%) reported that the vaccine had been recommended to them by a health-care provider. Seventy-six percent of the 169 persons were vaccinated, compared with 6% of persons who did not report receiving a recommendation (Table 2) (PR = 12.5, 95% CI 8.4, 18.6). The association of vaccination and recommendation was present for both races.

One hundred thirty-seven (36%) of the 381 respondents who were aware of the pneumococcal vaccine reported negative attitudes toward it (i.e., that the vaccine would not prevent pneumonia or that the vaccine would make them sick). Thirty-three percent of respondents with negative attitudes who answered the question and 44% of those with positive attitudes reported being vaccinated (PR = 0.8, 95% CI 0.6, 1.0). Respondents with negative attitudes who reported that the vaccine was recommended by a health-care provider were more likely to report being vaccinated (64%) than were those who did not report receiving a recommendation (5%) (PR = 12.5, 95% CI 5.9, 26.6). Eighty-four percent of persons with positive attitudes who received vaccination recommendations from health-care providers reported being vaccinated, compared with 7% of those with positive attitudes who did not receive a recommendation (Table 2) (PR = 12.3, 95% CI 7.7, 19.6).

Reported by: AJ Sievert, MD, Div of Physical Health, GN Bohan, MD, DeKalb County Board of Health; WR Elsea, MD, Fulton County Health Dept; RK Sikes, DVM, State Epidemiologist, Georgia Dept of Human Resources. Div of Field Svcs, Epidemiology Program Office; Div of Immunization, Center for Prevention Svcs; EIS Class of 1988, CDC (MMWR vol 37, No. 42).

CDC Editorial Note: As many as 20,000 influenza-associated deaths occur during typical influenza epidemics, and approximately 40,000 deaths associated with pneumococcal infections occur each year. Many of the deaths are in persons at high risk for serious complications from these illnesses, particularly persons aged greater than or equal to 65 years.[1] Although safe, effective, and inexpensive vaccines are available for these diseases, only about 22% of persons greater than or equal to 65 years of age receive influenza vaccine annually; only 10% have ever received pneumococcal vaccine.[1] Limited data have suggested that lack of awareness of the availability and benefits of safe, effective vaccines and unfounded concerns about adverse reactions among both physicians and patients contribute to low levels of adult immunization.[1] Many of the DeKalb County and Fulton County residents interviewed were unaware of the availability of vaccines against influenza (10%) and pneumococcal disease (47%), and many expressed negative attitudes toward the safety and effectiveness of these vaccines. Other factors influencing vaccinations in this group need to be identified.

These data have several important limitations. The survey addressed a limited segment of the population at high risk for complications from influenza and pneumococcal infections in metropolitan Atlanta. Persons less than 65 years of age with high-risk conditions such as cardiopulmonary disease, those who do not live in residential centers, and those living in chronic-care facilities were not included. Of persons who were surveyed, 85% were women, a disproportionately high percentage compared with the percentages of women greater than or equal to 65 years of age living in DeKalb (64%) and Fulton (65%) counties. The racial distributions of respondents from both DeKalb and Fulton counties also differed from that of the reference populations (Table 1). Selection bias may have been introduced into this survey because residential centers voluntarily participated in the survey, and randomization was not possible. In addition, the analysis is potentially complicated by the lack of information on the number of respondents seen by health-care providers. Those not seen by providers are unlikely to have received vaccination recommendations. Also, responses concerning immunization status were not verified. However, in previous surveys on the use of influenza vaccine, respondents correctly recalled receiving a "flu shot" within the previous year (CDC, unpublished data, 1988).

Despite these limitations, findings in this survey were similar to others[1] in demonstrating that recommendations for vaccination from health-care providers markedly influenced the decision to be vaccinated, even among those with negative attitudes toward immunization. Health-care providers can promote adult immunization by increasing awareness of vaccine availability, safety, and effectiveness and by recommending and offering vaccines to all adults, whenever indicated. Providers often miss opportunities to immunize adults during routine contacts in offices, clinics, and hospitals[1]; such opportunities can be used to review the immunization status of adult patients and, when indicated, provide influenza and pneumococcal vaccines as well as other appropriate vaccines (diphtheria and tetanus toxoids, measles-mumps-rubella, and hepatitis B vaccines).[2,3] Many persons are candidates for both influenza and pneumococcal vaccines, and these vaccines can be given simultaneously.[4,5] Education of health-care providers should therefore emphasize increasing awareness of not only vaccine recommendations but also the provider's role in promoting adult immunization.

References

1. Williams WW, Hickson MA, Kane MA, Kendal AP, Spika JS, Hinman AR. Immunization policies and vaccine coverage among adults: the risk for missed opportunities. Ann Intern Med 1988;108:616-25.
2. ACIP. Adult immunization: recommendations of the Immunization Practices Advisory Committee. MMWR 1984;33(suppl 1S).
3. Committee on Immunization. Guide for adult immunization. Philadelphia: American College of Physicians, Council of Medical Societies, 1985.
4. ACIP. Prevention and control of influenza. MMWR 1988;37:361-4,369-73.
5. ACIP. Update: pneumococcal polysaccharide vaccine usage—United States. MMWR 1984;33:273-6,281.

In Other AMA Journals

JAMA
Black Student Enrollment in US Medical Schools
S. M. Lloyd, Jr; R. L. Miller (*JAMA*. 1989;261:272)

NEW Triaminic® Nite Light™

For 8 full hours of nighttime cough relief for children...

Helps children with coughs and colds get the rest they need...and helps parents rest easier!

Now, a single bedtime dose of new Triaminic NITE LIGHT is all it takes for 8 hours of relief from persistent nighttime cough—often the most troublesome symptom a child suffers.

The maximum pediatric dose of dextromethorphan helps ease nighttime cough while a decongestant and an antihistamine temporarily relieve other cold symptoms that can deprive a child of much-needed sleep.

Recommend Triaminic® NITE LIGHT,™ a good night from Triaminic®

SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division

01882R

© 1989 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936

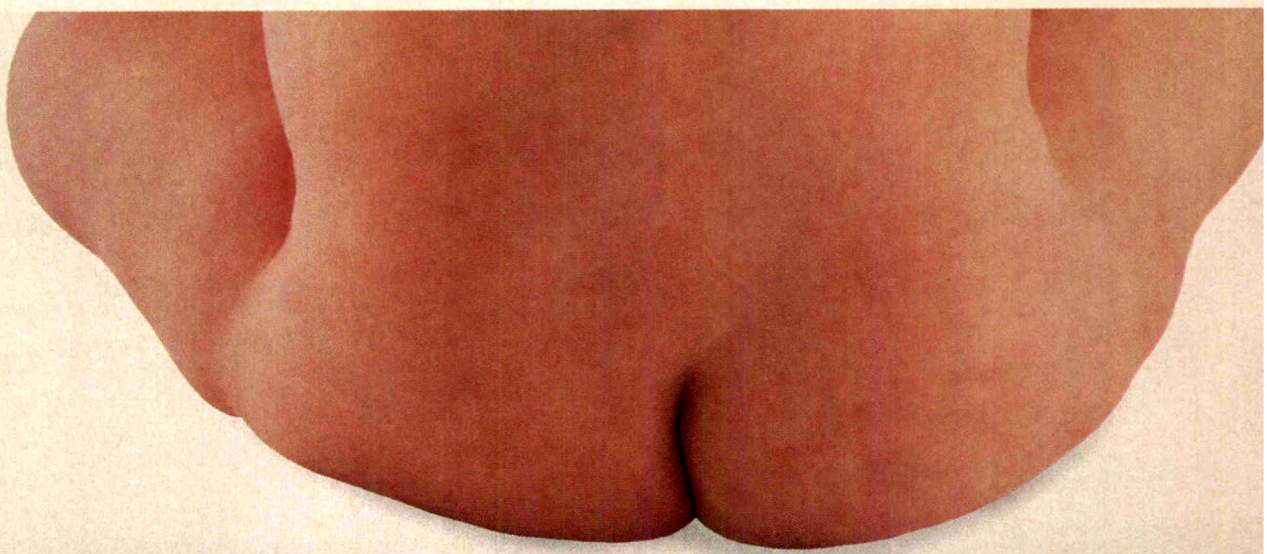
CONTEMPO INTERFACE '89

Survey the year's key medical advances and exchange ideas with leading physicians across the medical spectrum. There's nothing like it in continuing medical education!

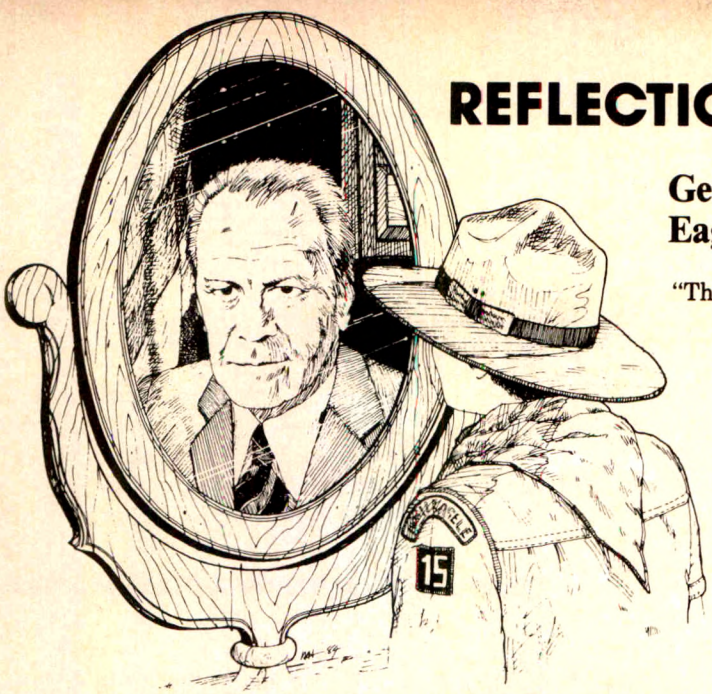
CONTEMPO

interface

Call 1-800-621-8335.
(In Illinois call collect,
1-312-645-4987.)



THERE'S NO REASON TO T



REFLECTIONS OF GREATNESS

Gerald Ford, President: 1974 - 1977. Eagle Scout, 1927.

"The child is father of the man." Wordsworth said it over one-hundred fifty years ago. The strengths ingrained in youth flourish with age.

For more than seventy years, the Boy Scouts have perpetuated the ideals of America: honor, character, loyalty; duty to God, mankind, and country.

It's not surprising some of our nations's outstanding citizens and leaders have been Boy Scouts.

BECOME A MEMBER OF THE NATIONAL BOY SCOUT ALUMNI FAMILY. JOIN TODAY!

Your one-year, $10 membership entitles you to the Alumni Bulletin, the Annual Report, a membership card and an attractive wall certificate suitable for framing.
A three-year, $30 membership entitles you to a free Norman Rockwell print, as well as all of the benefits of a one-year membership.

Write today to:

National Boy Scout Alumni Family
1325 Walnut Hill Lane • Irving, Texas 75062 - 1296

AT A CHILD LIKE AN ADULT.

Diaper rash is often treated with the same medications used to treat athlete's foot. The safety and efficacy of these more potent steroid/antifungal combinations, such as Lotrisone® (clotrimazole, USP and betamethasone dipropionate, USP),† have not been established in children under the age of 12.[1] Mycolog®-II, however, has been proven clinically effective even in children as young as 2 months old.[2] Mycolog-II. It's the right way to treat a child.

Please see next page for Brief Summary of Prescribing Information.

References: 1. Lotrisone full Prescribing Information. 2. Mycolog-II full Prescribing Information.

The combination steroid/antifungal specifically indicated for cutaneous candidiasis.

MYCOLOG®-II D.A.W.*

(nystatin and triamcinolone acetonide cream, USP)

*Dispense as written.
†Lotrisone is a registered trademark of Schering Corporation, USA.

Innovation in topical delivery

SQUIBB

YCOLOG®-II
ystatin and Triamcinolone Acetonide Cream USP and Ointment
r Dermatologic Use Only
t for Ophthalmic Use

ESCRIPTION: MYCOLOG-II Cream and Ointment (Nystatin and Triamcinolone cetonide Cream USP and Ointment) for dermatologic use provide 100,000 its of the antifungal agent nystatin and 1.0 mg of the synthetic corticosteroid amcinolone acetonide per gram.

ONTRAINDICATIONS: This preparation is contraindicated in those patients th a history of hypersensitivity to any of its components.

RECAUTIONS: General—Systemic absorption of topical corticosteroids has oduced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, anifestations of Cushing's syndrome, hyperglycemia, and glucosuria in me patients.

Conditions that augment systemic absorption include application of the ore potent steroids, use over large surface areas, prolonged use, and the ldition of occlusive dressings.

Therefore, patients receiving a large dose of any potent topical steroid plied to a large surface area should be evaluated periodically for evidence of PA axis suppression by using the urinary free cortisol and ACTH stimulation sts, and for impairment of thermal homeostasis. If HPA axis suppression or evation of the body temperature occurs, an attempt should be made to thdraw the drug, to reduce the frequency of application, or to substitute a ss potent steroid.

Recovery of HPA axis function and thermal homeostasis are generally ompt and complete upon discontinuation of the drug. Infrequently, signs and mptoms of steroid withdrawal may occur, requiring supplemental systemic rticosteroids.

Children may absorb proportionally larger amounts of topical cortico- eroids and thus be more susceptible to systemic toxicity (see PRECAU- ONS, Pediatric Use).

If irritation or hypersensitivity develops with the combination nystatin and amcinolone acetonide, treatment should be discontinued and appropriate erapy instituted.

aboratory Tests—If there is a lack of therapeutic response, appropriate micro- ological studies (e.g., KOH smears and/or cultures) should be repeated to nfirm the diagnosis and rule out other pathogens, before instituting another urse of therapy.

A urinary free cortisol test and ACTH stimulation test may be helpful in aluating hypothalamic-pituitary-adrenal (HPA) axis suppression due to rticosteroid.

rcinogenesis, Mutagenesis, and Impairment of Fertility—Long-term ani- al studies have not been performed to evaluate carcinogenic or mutagenic otential, or possible impairment of fertility in males or females.

egnancy Category C—There are no teratogenic studies with combined ystatin and triamcinolone acetonide. Corticosteroids are generally teratogenic laboratory animals when administered systemically at relatively low dosage vels. The more potent corticosteroids have been shown to be teratogenic after rmal application in laboratory animals. Therefore, any topical corticosteroid eparation should be used during pregnancy only if the potential benefit stifies the potential risk to the fetus.

Topical preparations containing corticosteroids should not be used exten- vely on pregnant patients, in large amounts, or for prolonged periods of time.

rsing Mothers—It is not known whether any component of this preparation excreted in human milk. Because many drugs are excreted in human milk, ution should be exercised during use of this preparation by a nursing oman.

diatric Use—In clinical studies of a limited number of pediatric patients nging in age from two months through 12 years, nystatin-triamcinolone eam formulation cleared or significantly ameliorated the disease state in most tients.

Pediatric patients may demonstrate greater susceptibility to topical rticosteroid-induced hypothalamic-pituitary-adrenal (HPA) axis suppres- on and Cushing's syndrome than mature patients because of a larger skin rface area to body weight ratio.

HPA axis suppression, Cushing's syndrome, and intracranial hypertension ve been reported in children receiving topical corticosteroids. Manifesta- ns of adrenal suppression in children include linear growth retardation, layed weight gain, low plasma cortisol levels, and absence of response to TH stimulation. Manifestations of intracranial hypertension include bulging ntanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the ast amount compatible with an effective therapeutic regimen. Chronic rticosteroid therapy may interfere with the growth and development of ildren.

VERSE REACTIONS: A single case (approximately one percent of patients udied) of acneform eruption occurred with use of combined nystatin and amcinolone acetonide in clinical studies.

Nystatin is virtually nontoxic and nonsensitizing and is well tolerated by all e groups, even during prolonged use. Rarely, irritation may occur.

The following local adverse reactions are reported infrequently with topical rticosteroids (reactions are listed in an approximate decreasing order of currence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, neform eruptions, hypopigmentation, perioral dermatitis, allergic contact rmititis, maceration of the skin, secondary infection, skin atrophy, striae, d miliaria.

VERDOSAGE: Topically applied corticosteroids can be absorbed in sufficient ounts to produce systemic effects (see PRECAUTIONS, General); however, ute overdosage and serious adverse effects with dermatologic use are likely.

OSAGE AND ADMINISTRATION: The use of these preparations should be scontinued if symptoms persist after 25 days of therapy (see PRECAUTIONS, boratory Tests). MYCOLOG-II Cream and Ointment should *not* be used with clusive dressings.

OW SUPPLIED: MYCOLOG-II Cream (Nystatin and Triamcinolone Acetonide eam USP) is supplied in 15 g, 30 g, and 60 g tubes and 120 g jars.
MYCOLOG-II Ointment (Nystatin and Triamcinolone Acetonide Ointment) is pplied in 15 g, 30 g, and 60 g tubes and 120 g jars.

orage—Store at room temperature; avoid freezing cream.

4-019A/ J4-024)

Innovation in topical delivery

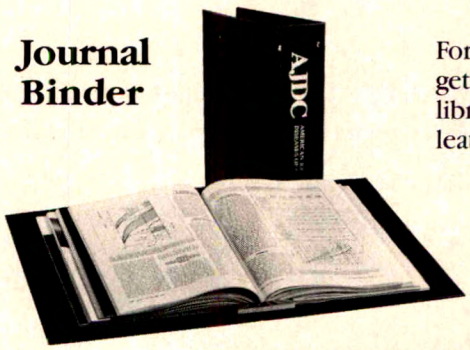
SQUIBB DERM

Preserve valuable scientific information

with these special *AJDC* binders and cases

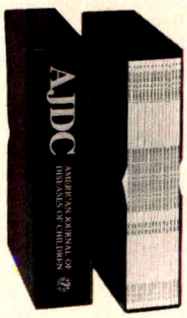
Preserve your issues of *AJDC* conveniently and attractively with these specially designed holders. Choose binder or case style; each holds 12 issues. Featuring gold-stamped lettering, on blue to match your journal cover.

Journal Binder



For convenient reference, get this attractive library binder in leatherette covering.

Journal Case



Easy-to-shelve, this library style case is durable and lasting.

To order yours today, just complete and mail this coupon.

AJDC
Department: AMA
Jesse Jones Industries
499 East Erie Avenue
Philadelphia, PA 19134

Please send me:

__ Binders @ $9.95 each (three/$27.95; six/$52.95)
__ Cases @ $7.95 each (three/$21.95; six/$39.95)

TOTAL $_____

PA residents add 6% sales tax.

☐ Enclosed is $_____. Add $1 per unit Postage and Handling. Outside USA $2.50 per unit (U.S. funds only.)

☐ Charge my: (Minimum $15)

☐ American Express ☐ Visa
☐ MasterCard ☐ Diners Club

Card #

Exp. Date

Signature

Toll Free # (charge orders only)
1-800-972-5858 (7 days, 24 hours)

Print Name

Address (No P.O. Box Please)

City/State/Zip

Satisfaction Guaranteed

Dexamethasone Therapy for Bacterial Meningitis in Infants and Children

The pathophysiological events that are believed to contribute to adverse outcome from bacterial meningitis include alteration of cerebral capillary endothelial cells that comprise the blood-brain barrier, cytotoxic and vasogenic cerebral edema, loss of autoregulation, and increased intracranial pressure.[1] These alterations can lead to a reduction in cerebral perfusion pressure and diminution in cerebral blood flow. This results in regional hypoxia and focal ischemia of brain tissue, possibly manifested as neurologic sequelae, learning or developmental disabilities, or communication disorders.

See also pp 290, 301, and 307.

A number of investigators are pursuing studies in experimental meningitis models to delineate the mechanisms involved in meningeal inflammation and how this response can be downregulated by dexamethasone phosphate and other drugs. Available evidence in experimental meningitis suggests that components of the bacterial cell wall (eg, lipooligosaccharide of *Haemophilus influenzae* type b and lipoteichoic acid of *Streptococcus pneumoniae*) that are elaborated in infection stimulate interleukin 1 (IL-1) and cachectin (tumor necrosis factor) production within the central nervous system.[1-5] These cytokines affect adversely capillary endothelial cell function, arachidonic acid metabolism, and cerebral blood flow. Dexamethasone modulates production of these cytokines which, in turn, lessens the meningeal inflammatory response.[2-4]

Dexamethasone has been shown to decrease significantly brain water content, intracranial pressure, and cerebrospinal fluid (CSF) lactate concentrations in animals experimentally infected with intracisternally administered *H influenzae* or *S pneumoniae*.[6-8] Dexamethasone given one hour before or simultaneously with *H influenzae* type b lipooligosaccharide reduced significantly tumor necrosis factor activity and meningeal inflammation in rabbits.[2] Experiments in rats showed that IL-1 and tumor necrosis factor can act synergistically in altering function of the cerebral capillary endothelium.

This results in the penetration of albumin labeled with iodine 125 from serum into CSF.[3] Additionally, dexamethasone lowered prostaglandin E_2 concentrations in CSF and decreased the leakage of some proteins from the serum into CSF in rabbits with experimental pneumococcal meningitis.[9,10] It is likely that many of these alterations also occur in infants and children with bacterial meningitis. We reported recently that IL-1 concentrations in CSF obtained after 24 hours of therapy were significantly lower in patients who received dexamethasone than in those given placebo.[11] The concentrations of IL-1 in CSF at that time correlated significantly with CSF protein, lactate, and glucose (inversely) concentrations and with the presence of neurologic sequelae on follow-up examinations in those children.

Results of corticosteroid therapy in experimental bacterial meningitis provided the basis for our three therapeutic trials of dexamethasone in infants and children with bacterial meningitis.[12,13]

RESULTS OF THE FIRST TWO CLINICAL TRIALS

The results of the first two placebo-controlled double-blind trials of dexamethasone therapy showed three beneficial effects of steroid treatment.[12] First, fever resolved more quickly in those patients receiving dexamethasone therapy (1.6 vs 5.0 days, $P<.001$). Second, the CSF concentrations of lactate and protein were significantly lower and of glucose significantly higher approximately 24 hours after the start of dexamethasone vs placebo therapy. Third, the incidence of bilateral moderate or greater hearing loss was significantly lower in the dexamethasone-treated patients (3 of 92 vs 13 of 84, $P<.01$) and fewer steroid-treated patients required hearing aids (1 of 92 vs 12 of 84, $P<.001$). The relative risk (95% confidence interval) of developing bilateral moderate or greater hearing impairment was 4.75 (1.60-14.08) and of requiring hearing aids, 13.14 (2.89-59.74), for placebo vs dexamethasone-treated patients. Because of differences in the rates of hearing impairment in these two clinical trials, a stratified analysis (Mantel-Haenzel method) of the data from the two studies considered separately showed that the relative risks (95% confidence intervals) were 2.54 (1.09-5.89) and 3.80 (1.40-10.32) for placebo vs dexamethasone-treated patients. This confirmed the validity of combining the data from the two studies.

COMBINED RESULTS OF THREE CLINICAL TRIALS

The number of patients studied in the third placebo-controlled, double-blind study was too small to achieve statistically significant differences in outcome for the two treatment groups.[13] When data from the three studies are combined, however, the beneficial effects of dexamethasone therapy are extended. A total of 260 patients have been evaluated. The number of seizures occurring after admission to the hospital was 10 of 133 for patients receiving dexamethasone therapy vs 21 of 127 for patients receiving placebo therapy ($P=.025$). Hemiparesis occurred in 3 of 133 dexamethasone-treated vs 11 of 127 placebo-treated patients ($P=.022$), and

Incidence Rates of Hearing Impairment in Infants and Children Who Had Bacterial Meningitis (Combined Data From Three Clinical Trials[12,13])

Results	Treatment Groups: Placebo (n=127)	Treatment Groups: Dexamethasone (n=133)	χ^2 Value (P Value)	Relative Risk*
No. of patients evaluated†	113	122	...	...
Mild or greater hearing loss in one or both ears, No. (%)	39 (35)	24 (20)	6.585 (.01)	1.8 (1.1-2.9)
Moderate or greater hearing loss in one or both ears, No. (%)	21 (19)	11 (9)	4.565 (.03)	2.1 (0.99-4.3)
Moderate or greater hearing loss bilaterally, No. (%)	15 (13)	4 (3)	7.887 (.005)	4.1 (1.3-12.2)
Hearing aids required, No. (%)	12 (11)	1 (1)	10.781 (.001)	13.0 (1.7-99.6)

*Values are the relative risk of developing hearing impairment in placebo- vs dexamethasone-treated patients (95% confidence interval).
†Repeated audiometric tests were performed from 3 to 12 months or more after illness in 24 dexamethasone- and 33 placebo-treated patients who had abnormal results on initial examinations (see text).

reactive arthritis occurred in 2 of 133 dexamethasone-treated patients vs 7 of 127 placebo-treated patients ($P=.077$).

At the six-week follow-up examination, neurologic abnormalities were found in 18 (14.6%) of 123 dexamethasone-treated children compared with 23 (20.2%) of 114 children given placebo therapy. Neurologic examinations were performed 1 year after illness in patients enrolled in the first two studies only. The rates of neurologic sequelae in those patients were 3 (4%) of 81 and 9 (12%) of 75 for those given dexamethasone and placebo, respectively ($P=.052$).

Audiometric evaluations have been performed in 235 patients (90%): 113 placebo-treated and 122 dexamethasone-treated patients. The other 25 patients, equally divided between the two study groups, were unavailable for audiometric tests. For 21 of these 25 patients, parental interviews or information gleaned from the patients' medical records suggested that all but 1 patient hears sufficiently well for normal language development 1 year or longer after the illness. One 20-month-old placebo-treated infant was considered to have delayed speech development 1 year after the illness. When various categories of hearing disability were assessed in the 235 patients, the relative rates of hearing impairment and the relative risks of developing abnormal hearing consistently and significantly favored dexamethasone over placebo therapy (Table).

DEXAMETHASONE EFFECT ACCORDING TO SEVERITY OF ILLNESS

We analyzed the data for the 260 study patients to determine whether one group of children responded more favorably to dexamethasone therapy than another. The rates of moderate or greater hearing loss in one or both ears (7 [9%] of 79 vs 12 [21%] of 56, $P=.039$) and in both ears only (1 [1%] of 79 vs 9 [16%] of 56, $P=.001$) were significantly smaller in dexamethasone-treated than in placebo-treated patients, respectively, with *Haemophilus* meningitis when the Herson and Todd[14] prognostic score was 2.5 or lower, indicating a milder illness. There was no difference in hearing outcome for the two treatment groups when the scores were greater than 2.5. Additionally, we showed that moderate or greater hearing impairment occurred significantly more often in those with an initial CSF glucose concentration of 1.1 mmol/L or lower (13 [12%] of 105 vs 6 [5%] of 130, $P=.03$), a finding consistent with the data of Dodge et al.[15] Bilateral moderate or greater hearing loss, however, occurred less often in those receiving dexamethasone therapy than those receiving placebo therapy, regardless of whether the initial CSF glucose concentration was 1.1 mmol/L or lower (3 [6%] of 53 vs 10 [19%] of 52, $P=.035$) or greater than 1.1 mmol/L (1 [1%] of 69 vs 5 [8%] of 61, $P=.067$).

We believe that the combined data from the three studies indicate that dexamethasone favorably affects the outcome of bacterial meningitis in infants and children by modulating the meningeal inflammatory response and by decreasing significantly the incidence of hearing impairment. Additionally, dexamethasone therapy is beneficial in those with milder illness, as reflected by Herson and Todd[14] prognostic scores of 2.5 or lower and by initial CSF glucose concentrations of greater than 1.1 mmol/L.

ADVERSE EFFECTS

Adverse effects of dexamethasone therapy were uncommon. Dexamethasone therapy was not associated with delayed sterilization of CSF cultures, and relapse of meningitis occurred in only one patient, a dexamethasone-treated child who had *H influenzae* meningitis.[12] The rate of relapse of *Haemophilus* meningitis (1 [0.96%] of 104 steroid-treated patients) was similar to the 0.8% rate observed in 708 patients with *Haemophilus* meningitis treated in Dallas, Tex, from 1969 to 1980 before initiation of those three studies.[16] Secondary fever occurred in approximately two thirds of the dexamethasone-treated patients and was low grade, 24 to 36 hours in duration, and not associated with adverse effects.

Two dexamethasone-treated patients developed gastrointestinal bleeding on the second and third days of steroid treatment. In both cases, results of coagulation studies were normal and blood transfusions were required. It was uncertain, however, whether the bleeding was a result of

dexamethasone therapy, of the infants' central nervous system disease, of both, or caused by other undefined factors. There were no other adverse effects observed among the 133 dexamethasone-treated patients in the three clinical trials.

In our three clinical trials, 17 patients were initially enrolled but were later excluded because a bacterial cause was never established. Dexamethasone therapy was administered for approximately 48 hours in 6 of these patients without complications.

OTHER CLINICAL INVESTIGATIONS

Together with Carla Odio, MD, at the National Children's Hospital, San Jose, Costa Rica, we are conducting a fourth placebo-controlled, double-blind trial of dexamethasone therapy in which almost half of the intended 100 study patients with meningitis have already been enrolled. Similarly designed studies have recently been initiated in Toronto, Canada (pediatric patients), and on the West Coast of the United States (collaborative study of adult patients). Additionally, we plan to initiate a fourth neonatal bacterial meningitis collaborative study in the spring of 1989 to evaluate dexamethasone therapy in infants younger than 6 weeks of age. The results of these trials should provide information that will help us formulate definitive recommendations for dexamethasone therapy in bacterial meningitis.

RECOMMENDATION

We believe that the advantages of dexamethasone therapy outweigh the possible disadvantages and that dexamethasone should be considered for treatment of bacterial meningitis in infants and children older than 2 months of age. If dexamethasone is used as adjunctive therapy, we believe that all patients should be treated at the time of diagnosis; those with milder illness should not be excluded.

On the basis of data in experimental meningitis,[4] it seems prudent to administer dexamethasone concomitantly with the first parenteral dose of antibiotics. We prefer ceftriaxone sodium or cefotaxime sodium for antimicrobial therapy; we have shown that cefuroxime therapy can be associated with delayed sterilization of CSF cultures and with an increased rate of hearing impairment.[17] It should be emphasized that, to date, the favorable effects of dexamethasone therapy have been observed only in patients with *H influenzae* meningitis; too few patients with meningococcal or pneumococcal meningitis have currently been treated to assess efficacy. Dexamethasone should not be used to treat suspected or proved aseptic or nonbacterial meningitis. Hemoglobin concentration measurements and stool examinations for occult blood should be performed regularly during dexamethasone therapy and the steroid therapy stopped if melena or gross blood is observed.

GEORGE H. MCCRACKEN, JR, MD
MARC H. LEBEL, MD
Department of Pediatrics
University of Texas
Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX 75235-9063

The authors thank Stephen R. Preblud, MD, Centers for Disease Control, Atlanta, Ga, for providing statistical analysis.

Dr Lebel is now with the Department of Pediatrics and Microbiology, University of Montreal, Canada.

References

1. Sande MA, Scheld WM, McCracken GH Jr. Summary of a workshop: pathophysiology of bacterial meningitis: implications for new management strategies. *Pediatr Infect Dis J.* 1987;6:1167-1171.

2. Mustafa M, Ramilo O, Beutler B, Hansen EJ, McCracken GM. Measurement of CSF cachectin (TNF alpha) activity in experimental *Haemophilus influenzae* type b meningitis. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 25, 1988; Los Angeles, Calif.

3. Wispelway B, Long JM, Castracane JM, Scheld WM. Cerebrospinal fluid interleukin-1 activity following intracisternal inoculation of *Haemophilus influenzae* lipooligosaccharide. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 26, 1988; Los Angeles, Calif.

4. Mustafa M, Ramilo O, Beutler B, Hansen EJ, McCracken GH Jr. Modulation of inflammation and cachectin (TNF) activity in relation to treatment of experimental *Haemophilus influenzae* type b meningitis. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 26, 1988, Los Angeles, Calif.

5. Riesenfeld-Orn I, Garcia-Bustos J, Hoffman M, Tuomanen E. Pneumococcal cell wall components induce interleukin-1 but not tumor necrosis factor production by human monocytes. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 26, 1988; Los Angeles, Calif.

6. Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis: alterations with penicillin and methylprednisolone. *J Clin Invest.* 1980;66:243-253.

7. Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis.* 1985;151:528-534.

8. Syrogiannopoulos GA, Olsen KD, Reisch JS, McCracken GH. Dexamethasone in the treatment of experimental *Haemophilus influenzae* type b meningitis. *J Infect Dis.* 1987;155:213-219.

9. Kadurugamuwa JL, Hengstler B, Zak O. Cerebrospinal fluid protein profile in experimental pneumococcal meningitis and its alteration by ampicillin and anti-inflammatory agents. *J Infect Dis.* 1989;159:26-34.

10. Tureen JH, Stella FB, Clyman RI, Mauray F, Sande MA. Effect of indomethacin on brain water content, cerebrospinal fluid white blood cell response and prostaglandin E_2 levels in cerebrospinal fluid in experimental pneumococcal meningitis in rabbits. *Pediatr Infect Dis J.* 1987;6:1151-1153.

11. Mustafa MM, Lebel MH, Ramilo O, Olsen KD, Beutler B, McCracken GH. Detection of interleukin-1β and cachectin in cerebrospinal fluid of infants and children with bacterial meningitis. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 25, 1988; Los Angeles, Calif.

12. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. *N Engl J Med.* 1988;319:964-971.

13. Lebel MH, Hoyt MJ, Waagner DC, Rollin NK, Finitzo T, McCracken GH. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. *AJDC.* 1989;143:301-306.

14. Herson VC, Todd JK. Prediction of morbidity in *Haemophilus influenzae* meningitis. *Pediatrics.* 1977;59:35-39.

15. Dodge PR, Davis H, Feigin RD et al. Prospective evaluation of hearing impairment as a sequela of acute bacterial meningitis. *N Engl J Med.* 1984;311:869-874.

16. Schaad VB, Nelson JD, McCracken GH. Recrudescence and relapse in bacterial meningitis of childhood. *Pediatrics.* 1981;67:188-195.

17. Lebel MH, Hoyt MG, McCracken GH. Comparative efficacy of ceftriaxone and cefuroxime for treatment of bacterial meningitis. *J Pediatr.* In press.

Dexamethasone for Children With Bacterial Meningitis

Should It Be Routine Therapy?

Although most older infants and children develop normally after an episode of bacterial meningitis, some have subtle to moderate neurologic sequelae such as learning problems and speech delay, or suffer devastating neurologic injury. Although prevention of the disease is the optimal way to prevent neurologic damage due to bacterial meningitis, prompt and appropriate antimicrobial therapy and supportive care are the currently available means to limit or minimize neurologic sequelae. Newer antibiotics such as the third-generation cephalosporins have much greater in vitro activity against *Haemophilus influenzae* type b and are associated with greater bactericidal activity in cerebrospinal fluid than are ampicillin sodium or chloramphenicol sodium succinate. Therefore, it was hoped that the outcome of treatment with the newer agents would be superior to that following therapy with ampicillin or chloramphenicol. However, in all comparative trials to date, the outcome of children treated with the third-generation cephalosporins has been the same as for those receiving conventional antibiotics.[1-3] One must realize that these comparative studies have involved less than 150 children treated with each new agent and the duration of follow-up has not been longer than 2 years after discharge. Thus, differences in subtle neurologic abnormalities such as academic performance or speech development are not likely to be detected between the study groups. Nevertheless, no comparative studies have documented any difference due to antibiotic therapy in the incidence of substantial sensorineural hearing loss, a sequela that can be detected reliably in most young children.

See also pp 287, 301, and 307.

Since the newer agents do not appear to decrease neurologic damage, investigators are focusing on non–antibiotic-related approaches to diminish neurologic sequelae of bacterial meningitis. One such approach has been to evaluate anti-inflammatory agents to modify the host response to infection that itself could contribute to neurologic damage.[4] For example, during meningitis, cytotoxic edema is produced by substances released not only by bacteria but also by white blood cells, which are toxic to cell membranes. White blood cells and the increased protein concentration in the cerebrospinal fluid (CSF) probably interfere with normal CSF reabsorption by arachnoid villi during meningitis.[5] Both cerebral edema and altered CSF hydrodynamics contribute to increased intracranial pressure, which adversely affects cerebral blood flow. Vasculitis of cerebral blood vessels may also impede or totally obstruct cerebral blood flow.

The pathogenesis of sensorineural hearing loss due to bacterial meningitis involves the development of labyrinthitis. Bacteria can directly invade the cochlea hematogenously via the stria vascularis or through the cochlear aqueduct, which provides a pathway between the CSF and perilymph.[6,7] Sensory elements of the cochlea are destroyed by the labyrinthitis. Ossification of the cochlea may develop and this appears to be more extensive after meningitis due to *Streptococcus pneumoniae* than that due to *H influenzae* type b.[8] Extensive ossification complicates the placement and perhaps diminishes the performance of a cochlear implant. Bacteria may also reach the cochlea via the internal auditory canal in association with inflammation of the eighth cranial nerve.

Both experimental and clinical studies indicate that dexamethasone diminishes the inflammatory response within the central nervous system during bacterial meningitis.[9-11] However, initial clinical studies failed to demonstrate any benefit for dexamethasone in the treatment of children with bacterial meningitis,[12,13] but no mention was made of hearing evaluation in these patients.[12,13] Lebel and associates,[11] from Southwestern Medical Center in Dallas, Tex, reassessed the value of dexamethasone as adjunctive therapy of bacterial meningitis in infants and children. The investigators should be congratulated for their two clinical trials, which were carefully designed and efficiently conducted and were reported recently in the *New England Journal of Medicine*.[11] These are difficult studies to complete and require an enormous investment of time as well as cooperation. The investigators found that in addition to cefuroxime sodium or ceftriaxone, the administration of 0.15 mg/kg per dose of dexamethasone sodium phosphate every 6 hours for the first 4 days of therapy was associated with a significant reduction ($P<.01$) in moderate to severe or profound bilateral hearing loss (15.5% in the placebo groups vs 3.3% in the dexamethasone groups when the two studies are combined). Specifically, children with meningitis due to *H influenzae* type b were the only patients for whom dexamethasone administration proved beneficial. Among these patients moderate or more severe bilateral hearing loss occurred in 11 (17.2%) of 64 patients in the placebo groups vs 2 (2.7%) of 73 patients in the dexamethasone groups ($P<.01$). At follow-up approximately 1 year after discharge, no other significant differences were noted in the two groups with respect to neurologic sequelae.

It is important to note that two dexamethasone-treated patients developed gastrointestinal tract bleeding severe enough to require transfusions of blood products. Two other children receiving dexamethasone had heme-positive stools without "overt"

bleeding. Apparently, two other children enrolled in the ceftriaxone study were excluded because gastrointestinal tract bleeding precluded further use of the study drug. Furthermore, one child who received dexamethasone in addition to cefuroxime had a positive CSF culture for *H influenzae* type b at the end of a 10-day course of therapy. The authors concluded that the benefits of routine administration of dexamethasone to children with bacterial meningitis for the first 4 days of antimicrobial therapy outweigh the possible risks.

The results of these studies are potentially very exciting since bacterial meningitis is a leading cause of acquired deafness in children in the United States and approximately 10% of hearing-impaired children in special education programs in the United States have hearing losses related to meningitis.[14] However, a number of questions raised by this study should be addressed before routine dexamethasone therapy is recommended. First, the incidence of moderate or more severe bilateral hearing loss in *H influenzae* type b meningitis in the combined placebo groups (17.2%) is high compared with several other prospective studies from around the country. Other investigators have reported that less than 5% of children with *H influenzae* type b meningitis have this degree of hearing impairment[1,3,15]; this statistic approximates that found for the steroid-treated children in the Dallas study. It is not clear why the authors have found such a high incidence of hearing loss in their patients, although it is possible that this relates to the use of cefuroxime. If the combined Dallas studies evaluating cefuroxime[11,16] are compared with those of ceftriaxone,[1,11,17] including only those patients receiving placebo from the most recent studies, 13 (8.1%) of 161 patients treated with ceftriaxone vs 10 (14.9%) of 67 of patients treated with cefuroxime suffered bilateral moderate or more severe hearing loss. It should be pointed out that cefuroxime has not been associated with a high incidence of hearing loss in other studies.[18] In addition, there were not enough children treated in the ceftriaxone trial to demonstrate any significant benefit for dexamethasone; which brings us to a second question. Assume dexamethasone does decrease hearing loss in bacterial meningitis treated with cefuroxime. Is the same true for other antibiotics such as cefotaxime sodium, ampicillin, penicillin G potassium, or chloramphenicol? One cannot assume this to be the case, particularly with respect to pneumococcal meningitis. This will be an especially important question to answer since in the future a greater percentage of patients with bacterial meningitis will have *S pneumoniae* as the etiologic agent if the efficacy of the newer Hib conjugate vaccines matches their immunogenicity in young children.

A third question concerns the effects of short-term dexamethasone administration to children with viral meningitis. Many young children with aseptic or viral meningitis present with a large number of white blood cells, predominantly polymorphonuclear leukocytes, in their initial CSF examination. They are likely to be treated with antibiotics for some time until their CSF and blood cultures prove to be sterile. Is a 2- or 3-day course of dexamethasone totally harmless in such children? The answer is unknown, but should be investigated before the administration of dexamethasone becomes part of the standard care of children with suspected bacterial meningitis.

Is the timing of the dexamethasone administration critical? In experimental models, dexamethasone has to be administered concomitantly or even before antibiotics to afford the maximum anti-inflammatory action.[18] This appears to relate to the release of endotoxin when the bacteria are lysed by the antibiotic. Endotoxin release stimulates the production of tumor necrosis factor by macrophages, which in turn augments the inflammatory response. One effect of dexamethasone is to decrease tumor necrosis factor production by the stimulated macrophages. If steroids are not administered until some time after the organisms are killed, the inflammatory response may not be altered. If this is the case, then one could not use certain factors, such as the initial CSF glucose concentration, to predict children who are at high risk for hearing loss and potentially avoid dexamethasone therapy in patients with a low risk for deafness. Unfortunately, the severity of illness at the time of initial diagnosis and treatment of *H influenzae* type b meningitis does not appear to correlate with the development of hearing loss.[19]

Finally, some authorities recommend 7 to 10 days of antimicrobial therapy for children with uncomplicated cases of bacterial meningitis. I would be very reluctant to treat a child with *H influenzae* type b or pneumococcal meningitis for only 7 days if dexamethasone is also being administered for 4 of these days. In the Dallas study, such children were treated for 10 days.

For now, I believe it is premature to recommend dexamethasone therapy routinely for children with bacterial meningitis. However, the Dallas study should stimulate further investigations to confirm their findings as well as to develop other innovative approaches to minimize the neurologic insults associated with bacterial meningitis.

SHELDON L. KAPLAN, MD
Department of Pediatrics
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030

References

1. Del Rio MA, Chrane D, Shelton S, McCracken GH Jr, Nelson JD. Ceftriaxone versus ampicillin and chloramphenicol for treatment of bacterial meningitis in children. *Lancet.* 1983;1:1241-1244.

2. Jacobs RF, Wells TG, Steele RW, Yamauchi T. A prospective randomized comparison of cefotaxime versus ampicillin and chloramphenicol for bacterial meningitis in children. *J Pediatr.* 1985;107:129-133.

3. Kaplan SL, Mason SK, Mason EO Jr, et al. Follow-up of prospective randomized trial of ampicillin or chloramphenicol versus moxalactam treatment of *Haemophilus influenzae* type b meningitis. *J Pediatr.* 1988;112:795-798.

4. Sande MA, Scheld WM, McCracken GH Jr, Meningitis Study Group: report of a workshop: pathophysiology of bacterial meningitis-implications for new management strategies. *Pediatr Infect Dis J.* 1987;6:1143-1171.

5. Scheld WM. Pathogenesis and pathophysiology of pneumococcal meningitis. In: Sande MA, Smith AL, Root RK, eds. *Bacterial Meningitis.* New York, NY: Churchill Livingstone Inc; 1985: 37-39.

6. Igarashi M, Saito R, Alford BR, et al. Temporal bone findings in pneumococcal meningitis. *Arch Otolaryngol Head Neck Surg.* 1974;99:79-83.

7. Wiedermann BL, Hawkins EP, Johnson GS, et al. Pathogenesis of labyrinthitis associated with *Haemophilus influenzae* type b meningitis in infant rats. *J Infect Dis.* 1986;153:27-32.
8. Eisenberg LS, Luxford WM, Becker TS, House WF. Electrical stimulation of the auditory system in children deafened by meningitis. *Otolaryngol Head Neck Surg.* 1984;92:700-705.
9. Tauber MG, Khayam-Baski, Sande MA: Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis.* 1985;151: 528-534.
10. Syrogiannopoulos GA, Olsen KD, Reish JS, et al. Dexamethasone in the treatment of experimental *Haemophilus influenzae* type b meningitis. *J Infect Dis.* 1987;155:213-219.
11. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. *N Engl J Med* 1988;319:964-971.
12. DeLemos RA, Haggerty RJ. Corticosteroids as an adjunct to treatment in bacterial meningitis: a controlled clinical trial. *Pediatrics.* 1969;44:30-34.
13. Belsey MA, Hoffpauir CW, Smith MH. Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of results. *Pediatrics.* 1969;44:503-513.
14. Wolff AB, Brown SC. Demographics of meningitis-induced hearing impairment: implications for immunization of children against *Hemophilus influenzae* type b. *Am Ann Deaf.* 1987; 131:26-30.
15. Dodge PR, Davis H, Feigin RD, et al. Prospective evaluation of hearing impairment as a sequela of acute bacterial meningitis. *N Engl J Med.* 1984;311:869-874.
16. Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, McCracken GH Jr. Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. *AJDC.* 1989;143:301-306.
17. Lin TY, Chrane DF, Nelson JD, McCracken GH Jr. Seven days of ceftriaxone therapy is as effective as ten days' treatment for bacterial meningitis. *JAMA.* 1985;253:3559-3563.
18. Mustafa M, Ramilo O, Beutler B, et al. Modulation of inflammation and cachectin activity in relation to treatment of experimental *Haemophilus influenzae* type b meningitis. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 25, 1988; Los Angeles, Calif.
19. Gary N, Powers N, Todd JK: Clinical identification and comparative prognosis of high-risk patients with *Haemophilus influenzae* meningitis. *AJDC.* 1989;143:307-311.

Prospective Reimbursement and Pediatric Services

The findings described by Munoz and colleagues[1] in this issue of *AJDC* are important for planning pediatric services. It should be remembered that diagnosis related groups (DRGs) were originally intended to be a management tool to compare utilization

See also p 312.

and costs of treatment in similar disease categories. In 1984, the federal government first applied DRGs as a reimbursement methodology for Medicare beneficiaries. Pediatric facilities were excluded along with other specific services. The exclusion from DRG reimbursement was based primarily on the DRG's lack of experience and their consequent inability to establish reasonable reimbursement.

Reasonable reimbursement for pediatric services is the key issue. The popularity of prospective payment among federal and state governments as well as other payers has placed greater pressure to include pediatric services under the same reimbursement scheme as services for adult patients. This practice, particularly in "all-payer" states, poses immediate problems for institutions providing pediatric services. These problems are especially threatening to tertiary care pediatric facilities. If DRG reimbursement continues uncorrected, there may well be long-term implications also.

The most immediate problem is the financial integrity of pediatric facilities. Chronic underfunding cannot be managed indefinitely. Hospitals are being barraged from all sides of the reimbursement equation. The study by Munoz et al[1] indicates that there is ever-increasing cost shifting and that other payers and consumers pay the underreimbursed state program share. I suggest that the problem is even more severe. State Medicaid programs have generally underfunded care for years and many hospitals now find themselves barely covering the marginal costs of Medicaid programs. Cost shifting has also occurred for years and there is now a lack of cost-shifting opportunities. More and more payers are attempting to limit their payments and insulate themselves from cost-shifting practices. Their reasons are sound but this does present a real dilemma for providers and certain other services. The time has come when all services must carry their own weight financially. The use of nonpediatric-specific DRG reimbursement for pediatric services is a short-sighted cost-saving measure that may have long-term implications.

Tertiary care pediatric facilities are particularly threatened. The types of pediatric cases referred to the tertiary care centers do not readily lend themselves to prospective reimbursement. The costs associated with these specialized cases have enormous variability and demand an ever-changing diagnostic and treatment process. Should the tertiary care facilities suffer severe economic hardship, there would be no one to fill in the gap. Pediatric facilities, particularly freestanding pediatric hospitals, are not known for their financial strength. Many of the best-known facilities would not be viable if it were not for substantial philanthropic support. Further fiscal constraints will adversely affect patient care in the short run but, more importantly, could have a disastrous effect on pediatric research initiatives and training programs.

Solutions to this dilemma are not readily apparent. It is probably safe to assume that prospective reimbursement by the DRG method will continue to expand. This necessitates that a truly reasonable pediatric reimbursement model be put into place. A modified version of the existing adult model should not be used just for the sake of expediency. Sufficient flexibility should be built into any system to address the full spectrum of services, from the most mundane treatments to the treatment of chronically and tragically ill children.

It is not surprising that the study by Munoz et al[1] shows a significant difference among payer groups. One must be careful in this interpretation. The differences, I believe, are not medical. Rather, the differences point

out a glaring social problem that has the greatest impact on children, particularly children covered by Medicaid programs. I suspect that the problem is not exclusively related to health care providers and reimbursement methodologies. What we see in the study by Munoz et al[1] is a secondary impact of social policy, or lack of social policy, on health care services and providers. The authors make a good point when they state that health care policy is being driven by health care financing. We seem unwilling to make social decisions that have a direct impact on health care expenditures. There is a misguided belief that improved efficiencies by and effectiveness of providers will negate the need to answer these very difficult societal questions. At best, our unwillingness will only postpone the answering of these questions. In the meantime, we are not doing any favors for the providers but, more importantly, we are being unfair to our pediatric patients who need our services the most.

The problem of reasonable reimbursement is a real one for providers and governments alike. On a case basis, providers say we are routinely underreimbursed. However, aggregate government outlays, both state and federal, have continued to increase. Providers have accepted that DRG-type prospective reimbursement will continue for the foreseeable future. In the case of pediatric services, we need to ensure that an appropriate prospective reimbursement model is implemented. In general, tertiary pediatric services are different. The National Association of Children's Hospitals and Related Institutions Inc, recently published the report *Highlights of Children's Hospitals, Patients, Services and Finances*,[2] which is a concise comparison of pediatric facilities with teaching and nonteaching facilities. The comparisons are striking. A quick review of this report puts the current DRG prospective reimbursement deficiencies in a clear perspective.

Munoz and colleagues[1] should be complimented for pursuing this topic. Their article should open up opportunities to address a broad range of analysis of pediatric programs and associated reimbursement models. It is just a beginning.

J. Verne Singleton
Chief Operating Officer
University of Arizona
Health Sciences Center
1501 N Campbell
Tucson, AZ 85724

References

1. Munoz E, Chalfin D, Goldstein J, Lackner R, Mulloy K, Wise L. Health care financing policy for hospitalized pediatric patients. *AJDC*. 1989;143:312-315.

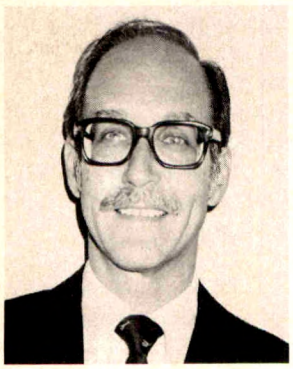
2. *Highlights of Children's Hospitals, Patients, Services and Finances*. Alexandria, Va: National Association of Children's Hospitals and Related Institutions Inc; 1988.

AJDC Is Moving . . .

As of April 1989, the AJDC editorial office will be located at Tulane University. After April 19, please address all correspondence, manuscripts, and inquiries to Vincent A. Fulginiti, MD, Editor, *AJDC*, Dean's Office, Room 1529, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; (504) 584-1989.

The Editorial Board Speaks . . .

Kenneth B. Roberts, MD



Ken has been with the journal for 9 years now and is one of our veteran Editorial Board members. As is true of many academicians, change is the order of the day, and is as expected as tomorrow. Last year Ken joined Evan Charney, MD, at the University of Massachusetts School of Medicine, Worcester, Mass, as a full professor of pediatrics. He directs inpatient pediatric services there. He already has embedded himself in the community by refereeing in the Worcester Youth Soccer Program. Ken has continued his interest in the febrile young infant, having published a number of articles in this area in recent years. He is now preparing the third edition of his popular book, *Manual of Clinical Problems in Pediatrics*, published by Little, Brown & Co Inc, Boston, Mass.

In 1988, Ken earned local and national awards for his activities in service to the youth of his community, and for furthering the goals of traffic safety in Maryland, the site of his last academic position.

THOUGHTS ON RESIDENCY EDUCATION, 1969-1989

Work-hour guidelines, pregnancy during residency, acquired immunodeficiency syndrome, due process, stress, support . . . the ponderings of a residency program director. I have been involved in residency education in one way or another for 20 years now, during which time there have been many changes. For fun, I made my list of changes affecting residencies from 1969 to 1989. Following are some of the items.

1. Training includes more: more behavior, more child development, more continuity practice, more adolescent medicine, more intensive care (neonatal and pediatric), and more subspecialty experience. (From where did the time come? Of what is there less?)

2. The "real world" intrudes on residency more now. The buffer period provided by the draft is gone, financial indebtedness is greater, and there is no on-campus resident housing community. I share with others the impression that spouses generally are less tolerant of the demands of residency now.

3. There is less opportunity to experience what is satisfying about "being the doctor." The pace of residency was never leisurely, but the turnover of patients was less rapid; length of stay has been compressed almost beyond our ability to establish rapport, let alone trust or respect. Those children and families who do stay in the hospital tend to become savvy veterans of the system.

4. The increasingly large number of women residents brings current issues in child bearing and child rearing home to pediatric programs, including pregnancy in the workplace and day-care, to name two. (What *do* I say to the honest resident who asked if I "mind" if she becomes pregnant during her next year of residency?)

5. There is more faculty supervision in many areas of the program. Along with this desirable change, however, has come a loss of resident independence and a more passive approach to learning.

6. The role of the senior supervising resident has diminished. This is due to a number of factors: increased involvement of faculty, the proliferation of subspecialists, and, perhaps, to differences in present-day PL-3s. In the era of pyramidal systems there was competition for third-year positions, including candidates returning from 2 years of practice experience in the service or from the equivalent of a research fellowship at the National Institutes of Health. Successively, the draft was eliminated, programs were obligated to provide 3 years of training for all incoming PL-1s, and residents were required to complete 3 years of training to be considered for certification by the American Board of Pediatrics. The PL-3s no longer were "elite," functioning essentially as junior faculty.

7. We now have complex new diseases that do not fit well with old ways of caring for patients, eg, bronchopulmonary dysplasia and acquired immunodeficiency syndrome. We also have new modes of treatment that devour care-giving resources, eg, neonatal intensive care and transplantation. Both bring new stresses.

8. There are more external influences and limitations on medical decision making, including health maintenance organizations, diagnosis related groups, and the like. (When did the term *bottom line* creep in?)

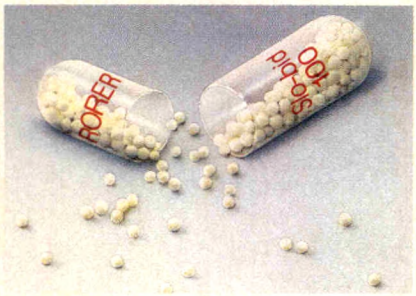
9. There is greater (and long-overdue) consideration given to curriculum, support systems, performance evaluation, and due process.

10. There is more creativity in residency curricula and more sharing of ideas both at meetings, particularly of the Ambulatory Pediatric Association, and in journals, such as *AJDC*.

There also are areas of (too) little change, such as the lack of meaningful roles for pediatric practitioners in residency education. These physicians, who are potential real-life role models for residents who aspire to be excellent practitioners, have little opportunity to show off what they do: their patients are treated out of view of residents and, when admitted to the hospital, are usually cared for by someone else, such as a subspecialist or surgeon. Residents could participate in selected community practices in a meaningful way; this is now occurring in a few programs around the country, including ours. (It is ironic that what makes the association between specialty-oriented departments and general pediatric practitioners so logical is, in effect, the recognition that the latter are subspecialists in community, office-based pediatric practice.)

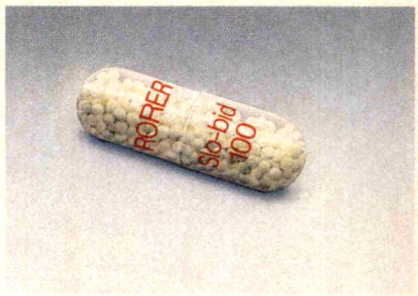
The list is not meant to be nostalgic nor to be negative about the present, just reflective. These are different times; some things are better, some things are not. As I mused about all of this, I spoke with Drs Evan Charney, Cathy DeAngelis, Steve Shelov, and Bob Adler, thoughtful and insightful individuals, who made their own lists. Most items were noted by everyone, but each of us had at least one additional issue. We now have a forum to continue these discussions, the Association of Pediatric Program Directors, and I am pleased: there is much to say—and to do.

Growing up on a steady theophylline is an open-and-shut case



Sprinkled

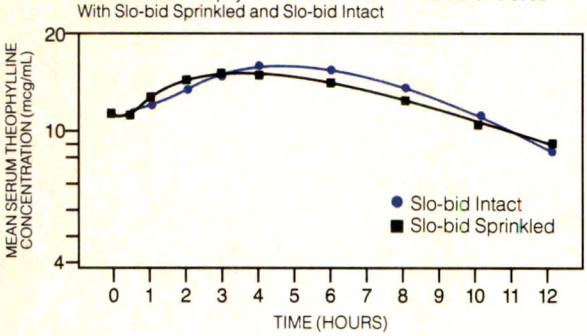
Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration[1]

Mean Serum Theophylline Concentration in 14 Children Dosed With Slo-bid Sprinkled and Slo-bid Intact



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.[2]

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in applesauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

In asthma and bronchitis

Slo-bid™ 12

(theophylline, anhydrous)

Nothing beats our system

From the makers of Azmacort™ (triamcinolone acetonide)

Please see next page for brief summary of prescribing information.

©1989 Rorer Pharmaceutical Corporation
Printed in U.S.A. FC#89-40 SB06189A 1/89

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA. U.S.A. 19034

Slo-bid™

(theophylline, anhydrous)
50 mg, 100 mg, 200 mg, and 300 mg

Gyrocaps®
Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 100 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 μg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 μg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects*. A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 μg/mL.

Information for Patients:
The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:
Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Rifampin	Decreased serum theophylline levels

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromotography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C – Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness of Slo-bid Gyrocaps administered:
1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

50 mg – Clear (cap) and opaque white (body) capsule with 50 printed in red
100 mg – Clear capsule with 100 printed in red
200 mg – Opaque white (cap) and clear (body) capsule with 200 printed in red
300 mg – Opaque white capsule with 300 printed in red

Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0057-99) and in unit dose 10 x 10 (NDC 0075-0057-62). Slo-bid Gyrocaps 100 mg are available in bottles of 100 (NDC 0075-0100-00), bottles of 1000 (NDC 0075-0100-99) and in unit dose 10 x 10 (NDC 0075-0100-62). Slo-bid Gyrocaps 200 mg are available in bottles of 100 (NDC 0075-0200-00), bottles of 1000 (NDC 0075-0200-99) and in unit dose 10 x 10 (NDC 0075-0200-62), and Slo-bid Gyrocaps 300 mg are available in bottles of 100 (NDC 0075-0300-00), bottles of 1000 (NDC 0075-0300-99) and in unit dose 10 x 10 (NDC 0075-0300-62), and are manufactured by:

RORER PHARMACEUTICALS
a division of
Rorer Pharmaceutical Corporation
Fort Washington, PA, U.S.A. 19034

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

Guarding the Guardians:

Research on
PEER REVIEW

The First International Congress on Peer Review in Biomedical Publication, to be held in Chicago, Illinois, May 10–12, 1989, will present original research on critical issues in the publication of scientific research. These will include

- the relationships between authors, editors, and reviewers, and how each is educated, selected, and evaluated
- analysis of editorial decision making
- publication bias
- journal practices and the testing of peer review
- quality assurance in biomedical research and publication
- the practical consequences of peer review

For more information on attending the Congress, contact Annette Flanagin, *The Journal of the American Medical Association*, 535 N Dearborn St, Chicago, IL 60610, (312) 280-7232.

"Work, Finish, Publish."
Michael Faraday

98% of subjects tested preferred EryPed*

Kristen thinks EryPed 200

"Tastes like strawberry."

How do you turn defiance into compliance?
Specify the erythromycin kids really like... EryPed.

- Available in delicious mixed-fruit or banana flavor
- Contains no dyes, artificial colors, or preservatives
- Requires no refrigeration
- Offers dosage flexibility—b.i.d., t.i.d., or q.i.d.†
- Can be taken with or without meals

*Data on file, Abbott Laboratories. Flavor evaluations conducted with 20 adult volunteers. Evaluations compared EryPed 200 and 400 to Barre's formulation of erythromycin ethylsuccinate oral suspension, USP 200 mg base/5 ml and 400 mg base/5 ml, respectively.

†q12h, q8h, or q6h.

There's no substitute for compliance

Write **EryPed® 200, 400 or Drops**

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Please see accompanying brief summary of prescribing information.

8113876

THE EXPANDED **EryPed**® LINE, FROM ABBOTT

ERYTHROMYCIN ETHYLSUCCINATE FOR ORAL SUSPENSION, USP

Brief Summary of Prescribing Information

DESCRIPTION: Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water. Erythromycin ethylsuccinate is an ester of erythromycin suitable for oral administration.

EryPed 200 and EryPed Drops (erythromycin ethylsuccinate for oral suspension) when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 ml (teaspoonful) or 100 mg per 2.5 ml (dropperful) with an appealing fruit flavor. EryPed 400 when reconstituted with water, forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 ml (teaspoonful) with an appealing banana flavor. After mixing, EryPed must be stored below 77°F (25°C) and used within 35 days; refrigeration is not required. These products are intended primarily for pediatric use but can also be used in adults.

Inactive Ingredients EryPed 200, EryPed 400 and EryPed Drops: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum, artificial flavors and other ingredients.

INDICATIONS: *Streptococcus pyogenes* (Group A beta hemolytic streptococcus): Upper and lower respiratory tract, skin, and soft tissue infections of mild to moderate severity.

Injectable benzathine penicillin G is considered by the American Heart Association to be the drug of choice in the treatment and prevention of streptococcal pharyngitis and in long-term prophylaxis of rheumatic fever.

When oral medication is preferred for treatment of the above conditions, penicillin G, V, or erythromycin are alternate drugs of choice.

When oral medication is given, the importance of strict adherence by the patient to the prescribed dosage regimen must be stressed. A therapeutic dose should be administered for at least 10 days.

Alpha-hemolytic streptococci (viridans group): Although no controlled clinical efficacy trials have been conducted, oral erythromycin has been suggested by the American Heart Association and American Dental Association for use in a regimen for prophylaxis against bacterial endocarditis in patients hypersensitive to penicillin who have congenital heart disease, or rheumatic or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.[1] Erythromycin is not suitable prior to genitourinary or gastrointestinal tract surgery. NOTE: When selecting antibiotics for the prevention of bacterial endocarditis the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]

Staphylococcus aureus: Acute infections of skin and soft tissue of mild to moderate severity. Resistant organisms may emerge during treatment.

Streptococcus pneumoniae (Diplococcus pneumoniae): Upper respiratory tract infections (e.g., otitis media, pharyngitis) and lower respiratory tract infections (e.g., pneumonia) of mild to moderate degree.

Mycoplasma pneumoniae (Eaton agent, PPLO): For respiratory infections due to this organism.

Hemophilus influenzae: For upper respiratory tract infections of mild to moderate severity when used concomitantly with adequate doses of sulfonamides. (See sulfonamide labeling for appropriate prescribing information). The concomitant use of the sulfonamides is necessary since not all strains of *Hemophilus influenzae* are susceptible to erythromycin at the concentrations of the antibiotic achieved with usual therapeutic doses.

Chlamydia trachomatis: For the treatment of urethritis in adult males due to *Chlamydia trachomatis.*

Ureaplasma urealyticum: For the treatment of urethritis in adult males due to *Ureaplasma urealyticum.*

Treponema pallidum: Erythromycin is an alternate choice of treatment for primary syphilis in patients allergic to the penicillins. In treatment of primary syphilis, spinal fluid examinations should be done before treatment and as part of follow-up after therapy.

Corynebacterium diphtheriae: As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

Corynebacterium minutissimum: For the treatment of erythrasma.

Entamoeba histolytica: In the treatment of intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

Listeria monocytogenes. Infections due to this organism.

Bordetella pertussis: Erythromycin is effective in eliminating the organism from the nasopharynx of infected individuals, rendering them non-infectious. Some clinical studies suggest that erythromycin may be helpful in the prophylaxis of pertussis in exposed susceptible individuals.

Legionnaires' Disease: Although no controlled clinical efficacy studies have been conducted, *in vitro* and limited preliminary clinical data suggest that erythromycin may be effective in treating Legionnaires' Disease.

CONTRAINDICATIONS: Erythromycin is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS: Erythromycin is principally excreted by the liver. Caution should be exercised in administering the antibiotic to patients with impaired hepatic function. There have been reports of hepatic dysfunction, with or without jaundice occurring in patients receiving oral erythromycin products.

Areas of localized infection may require surgical drainage in addition to antibiotic therapy.

Recent data from studies of erythromycin reveal that its use in patients who are receiving high doses of theophylline may be associated with an increase of serum theophylline levels and potential theophylline toxicity. In case of theophylline toxicity and/or elevated serum theophylline levels, the dose of theophylline should be reduced while the patient is receiving concomitant erythromycin therapy.

Usage during pregnancy and lactation: The safety of erythromycin for use during pregnancy has not been established.

Erythromycin crosses the placental barrier. Erythromycin also appears in breast milk.

ADVERSE REACTIONS: The most frequent side effects of erythromycin preparations are gastrointestinal, such as abdominal cramping and discomfort, and are dose related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections occur, the drug should be discontinued and appropriate therapy instituted.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis have occurred.

There have been isolated reports of reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

HOW SUPPLIED: EryPed 200 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 100 ml (**NDC** 0074-6302-13), 200 ml (**NDC** 0074-6302-53), and 5 ml unit dose in ABBO-PAC® packages (**NDC** 0074-6302-05). Each 5 ml (teaspoonful) of reconstituted suspension contains activity equivalent to 200 mg erythromycin.

EryPed 400 (erythromycin ethylsuccinate for oral suspension, USP) is supplied in bottles of 60 ml (**NDC** 0074-6305-60), 100 ml (**NDC** 0074-6305-13), 200 ml (**NDC** 0074-6305-53), and 5 ml unit dose in ABBO-PAC packages (**NDC** 0074-6305-05). Each 5 ml (teaspoonful) of reconstituted suspension contains activity equivalent to 400 mg erythromycin.

EryPed Drops (erythromycin ethylsuccinate for oral suspension) is supplied in 50 ml bottles (**NDC** 0074-6303-50). Each 2.5 ml dropperful (1/2 teaspoonful) of reconstituted suspension contains activity equivalent to 100 mg of erythromycin.

After reconstitution, EryPed must be stored below 77°F (25°C) and used within 35 days; refrigeration not required.

REFERENCE: 1. American Heart Association. 1977. Prevention of bacterial endocarditis. Circulation 56: 139A-143A.

8113876

Abbott Laboratories
North Chicago, IL60064

CEJKA IS NOT A SWEDISH GAME SHOW

But you may have heard of us. For nearly ten years, Cejka (CHECK'-A) & Company has been retained by clients nationwide for thoughtful and thorough physician search.

Several PEDIATRIC searches are now in progress exclusively through Cejka for practices in:

CALIFORNIA	TEXAS
ILLINOIS	MISSOURI
OKLAHOMA	NEVADA
FLORIDA	NEW MEXICO

GET TO KNOW US

Inquiries are confidential, and all fees/ expenses are paid by our clients. Call:

Julie Woolsey
CEJKA & COMPANY
222 South Central
St. Louis, MO 63105
1-800-365-2237

Southeast USA
(Academic Pediatrician Wanted)

Alabama Board Certified or Board Eligible Academic Pediatrician, Assistant Professor. Teaching medical students and family practice residents, direct patient care and clinical research interests are required.

Direct inquiries with C.V. to:
David C. Hefelfinger, M.D.
Dept. of Pediatrics
700 University Blvd.
East, Tuscaloosa,
Alabama 35401
(205)348-1304

Equal Opportunity Affirmative Action Employer.

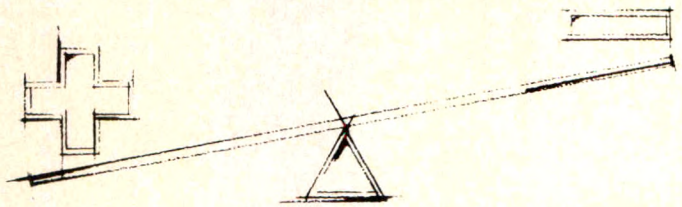
IF DIABETES IS A DISEASE YOU CAN LIVE WITH, WHY DID 150,000 DIE LAST YEAR?

Support the Research of the American Diabetes Association

American Diabetes Association®

Risk Management Resources at Your Fingertips

Today, the challenge for physicians and health care institutions to maintain and improve the quality of care is greater than ever. The changing environment of medicine increasingly demands innovative responses from the profession. And, increasingly, physicians and institutions are responding.

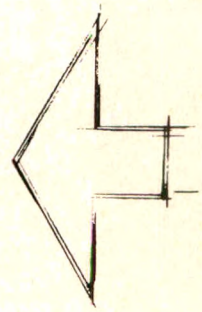


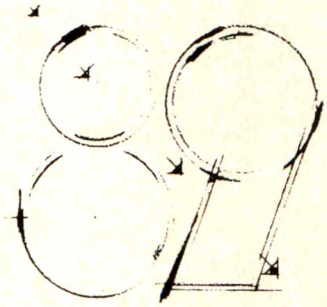
The *Compendium of Patient Safety and Medical Risk Management Programs* is a comprehensive listing of patient safety/risk management resources available from the AMA/Specialty Society Medical Liability Project, the American Medical Association, the Council of Medical Specialty Societies, the Physician Insurers Association of America, national medical specialty organizations and state medical associations.

Featuring Capsule Program Descriptions and Complete Index

This is a one-of-a-kind compilation, a uniquely comprehensive guide to such resources as:

Guidelines and policy statements · Committee and task force activities · Courses and seminars · Self-assessment programs · Data banks · Research projects · Publications, from manuals and books to newsletters and pamphlets · Clearinghouses, resource centers, bibliographies · Videotapes, audiotapes, slide programs





Purchase Includes Periodic Updates

To order, complete the order form below, or for VISA and MasterCard orders call toll-free **1-800-621-8335** (In Illinois, call collect 312-645-4987)

Order Form

Mail to:
American Medical Association
Book & Pamphlet Fulfillment OP140
P.O. Box 10946
Chicago, Illinois 60610-0946

YES, please send
The Compendium of Patient Safety and Risk Management Programs, OP140
3-ring binder, approximately 175 pp.

Name

Institution Group/Company

Address

City State Zip code

Send _____ copies @ $50.00 per copy ..... $_____

Add sales tax in CA, DC, IL and NY ..... $_____

Total amount due ..... $_____

☐ Enclosed is my check in the above total amount due payable to the American Medical Association.

☐ Please charge my ☐ Master Card ☐ VISA

Card Number Expiration date

Cardholder's signature Area code and telephone no.

A grape new way to help raise compliance!

New Grape Flavor
CHILDREN'S
TYLENOL®
acetaminophen
ELIXIR

First choice for fever and pain relief

Now...a choice of two great-tasting elixirs to promote even better dosage compliance

Because children often prefer one flavor over another, TYLENOL® offers them a choice: New Grape joins original Cherry Elixir to help improve acceptance and encourage compliance.[1] And, as you know, better compliance helps assure optimal efficacy.

Proven equally effective as aspirin for fever and pain relief[2,3] with a superior safety profile,[4] alcohol-free Children's TYLENOL® Elixirs come with a calibrated dosage cup for easy, accurate administration.

To help raise patient compliance in your practice, recommend the only brand that offers two elixir flavors—Children's TYLENOL®.

References: 1. Data on file, McNeil Consumer Products Company. **2.** Tarlin L, et al: *Am J Dis Child* 1972;124:880-882. **3.** Cooper SA: *Arch Intern Med* 1981;141:282-285. **4.** Aspirin or paracetamol? *Lancet* 1981;II:287-289.

© McN, 1988

McNeil Consumer Products Company
Fort Washington, PA 19034

McNEIL

Articles

Magnetic Resonance Imaging and Dexamethasone Therapy for Bacterial Meningitis

Marc H. Lebel, MD; M. Jean Hoyt, RN; David C. Waagner, MD;
Nancy K. Rollins, MD; Terese Finitzo, PhD; George H. McCracken, Jr, MD

• We conducted a third placebo-controlled, double-blind study of dexamethasone as adjunctive therapy for bacterial meningitis. Thirty-one patients received cefuroxime sodium (300 mg/kg per day in 3 doses) and dexamethasone phosphate (0.6 mg/kg per day in 4 doses for 4 days), and 29 received cefuroxime and placebo. The groups were comparable at the beginning of therapy. Magnetic resonance imaging performed between days 2 and 5 of therapy was used to assess brain water content indirectly. There were no differences between the 2 treatment groups with respect to the T_1- or T_2-weighted images. Fifty-two patients (88%) had normal magnetic resonance images; 5 patients had parietal or bifrontal extra-axial fluid collections, and 2 children had areas of abnormal signal intensity in the brain on T_2-weighted images. Abnormal findings on magnetic resonance imaging did not alter clinical management, and there was no correlation between the results of magnetic resonance imaging and the outcome of meningitis. The number of patients in this study was too small to determine any statistically significant differences in rates of hearing impairment; however, the cerebrospinal fluid findings and clinical outcome in dexamethasone-treated patients further support the previously reported beneficial effect of corticosteroid treatment in patients with bacterial meningitis.

(*AJDC.* 1989;143:301-306)

Despite the availability of antimicrobial agents with superior cerebrospinal fluid (CSF) bactericidal activity against meningeal pathogens and the availability of pediatric intensive care units, the morbidity associated with bacterial meningitis in infants and children remains high. It is unlikely that more active antimicrobial agents will alter the course and outcome of patients treated for this disease. Recent evidence suggests that the host's inflammatory response can adversely affect the neurologic outcome and that downregulation of cytokine production in the CSF is associated with modulation of CSF inflammation and improved outcome.[1-4]

We showed that dexamethasone decreased brain water content, intracisternal pressure, and CSF lactate concentrations in the experimental lapine model of *Haemophilus influenzae* type b meningitis.[5] In two placebo-controlled, double-blind trials of dexamethasone therapy for bacterial meningitis in infants and children, those who received steroid therapy had significantly improved findings on CSF examination 24 hours after the start of therapy and a significantly lower incidence of bilateral moderate to profound hearing impairment.[4]

See also pp 287, 290, and 307.

The purposes of this study were to determine whether the beneficial effects of dexamethasone therapy were associated with a diminution in brain water content as assessed by magnetic resonance imaging (MRI) and to assess the role and usefulness of MRI in the evaluation and therapy of patients treated for bacterial meningitis.

PATIENTS AND METHODS

Patients

Infants and children admitted to Children's Medical Center or Parkland Memorial Hospital, Dallas, Tex, with suspected or proved bacterial meningitis were eligible for the study if they were between 3 months and 16 years of age. Informed written consent was obtained from the parents or legal guardians of all children enrolled in the study. The study protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. Previous treatment with orally administered antibiotics or with one dose of a parenterally administered antibiotic did not preclude enrollment. Patients with known hypersensitivity to β-lactam antibiotics, with congenital or acquired abnormality of the central nervous system, or with a prosthetic device of the central nervous system were excluded from the study. Sixty-one patients were enrolled in the study. No patients had CSF or clinical findings compatible with the diagnosis of aseptic meningitis.

Therapy

All patients were treated with 100 mg/kg of cefuroxime sodium intravenously every 8 hours (300 mg/kg per day) for a minimum of 7 days for *Neisseria meningitidis* infections and for a minimum of 10 days for other pathogens.

On the basis of a computer-generated list of random therapy assignments, dexamethasone phosphate or placebo (two thirds normal saline) was given in a double-blind manner to all patients enrolled in the study. The dosage of dexamethasone phosphate was 0.6 mg/kg per day divided in 4 doses every 6 hours for the first 4 days of therapy. The first dose was given concurrently with or within the first 12 hours of the first dose of parenteral antibiotic. The code was not broken until the last 6-week follow-up was completed.

Laboratory Studies

All patients had examinations and cultures of CSF at diagnosis and again after approximately 24 hours of therapy. All CSF specimens were routinely cultured in the clinical microbiology laboratory on blood and chocolate agar plates and in thioglycolate broth. Cerebrospinal fluid obtained at 24 hours was also cultured in our research laboratory after the addition of cephalosporinase (Sigma Chemical Co, St Louis, Mo) to inactivate residual cefuroxime activity. Antimicrobial susceptibilities of the pathogens isolated from CSF and blood cultures were deter-

Accepted for publication January 11, 1989.

From the Departments of Pediatrics (Drs Lebel, Waagner, and McCracken and Ms Hoyt) and Radiology (Dr Rollins), The University of Texas Southwestern Medical Center at Dallas, Southwestern Medical School; and the Neuroscience Research Center, Dallas (Dr Finitzo). Dr Lebel is currently with the Departments of Pediatrics and Microbiology, University of Montreal, Canada.

Reprints not available.

mined by disk diffusion and by conventional broth dilution methods.

Follow-up Examinations

Daily examinations were performed during the time of hospitalization to assess the clinical course of illness, and a neurologic follow-up examination was performed 6 weeks after discharge.

Hearing Evaluation

Audiometric assessment was done within 6 weeks of hospital discharge using either audiometry brain-stem response or age-appropriate behavioral measures. Auditory brain-stem responses were elicited for each ear separately by a 100 μs rarefaction click transduced by a TDH49 earphone (CA1000 or Compact Four Unit, Nicolet Instrumentation Corp, Plano, Tex). Stimuli were presented at 20, 30, 60, and 80 dB HL. If a wave V response was not detected at these intensities, additional testing was undertaken to elicit a wave V threshold response in each ear. All the tests were read by one of us (T.F.), who was unaware of the therapy received by the patients. Whenever possible, repeated hearing evaluations were performed in those with abnormal audiograms 3 to 6 months after the first examination. The following classification was used to grade the degree of hearing loss: no response at 30 or 40 dB, mild; 50 or 60 dB, moderate; 80 or 90 dB, severe; and 100 or 105 dB, severe to profound.

Statistical Analysis

The Mann-Whitney U test was used to assess differences between numerical variables for the placebo and dexamethasone groups. The χ^2 statistic was used to compare the two groups for variables such as demographic characteristics and clinical outcome. When 20% or more of the expected number of observations was less than five, Fisher's Exact Test was used. Pearson correlation coefficients were used to determine the relationships between brain water content indexes obtained by MRI and age, duration of illness, and day of performance of the examination. A statistical level of $P<.05$ was considered significant.

MRI

Magnetic resonance images were obtained using a 0.35 T superconducting magnet (Diasonics, Milpitas, Calif). Axial spin-echo images were obtained with a 20 cm field-of-view head coil, 256×256 image matrix, 0.95 mm pixel size, 2 to 4 excitations, and 10 mm slice thickness with no interslice gap. Repetition times were 2000 and 500 ms, and the time to echo was 30 ms. Tissue profiles consisting of T_1 (in milliseconds), T_2 (in milliseconds), and hydrogen density (concentration) were calculated as follows. Using the computer cursor, a region of interest was drawn freehand in the gray matter of the right frontal pole, taking care to exclude the CSF in the regional sulci. Similarly, regions of interest were also defined in the white matter of the right frontal lobe and left parietal occipital lobes as well as the gray matter of the parietal occipital region. The computer automatically calculated the tissue indexes for the defined regions of interest, provided that the imaging profiles for both the T_1- and T_2-weighted sequences, including attenuation, gain, and the center slice, were identical. Although technically optimal images were obtained in all cases, calculation of tissue indexes could not be performed in nine patients because the imaging parameters for both the T_1- and T_2-weighted sequences were found not to be identical during postacquisition image calculations.

Magnetic resonance image evaluation was performed for every patient between day 2 and day 5 (mean, day 3) of medical therapy. Most patients were sedated using a single oral dose of chloral hydrate, 50 to 80 mg/kg. Patients weighing more than 12.5 kg were given sodium pentobarbital, 4 mg/kg, intramuscularly for sedation.

At the discretion of the patients' physicians, computed tomographic (CT) scans of the head were performed, but only when clinically indicated.

Table 1.—Demographic and Clinical Characteristics of Study Patients at the Time of Admission to the Hospital*

	Drug Treatment Group	
	Placebo (n=29)	Dexamethasone (n=31)
Age, mo†	18.5±20.2	13.8±12.8
Median	9	10
Range	3-76	3-71
Sex, No. of patients		
M	16	21
F	13	10
Race, No. of patients		
W	15	16
B	6	8
Hispanic	8	7
Duration of illness, h†	36.6±25.7	36.9±22.9
Clinical score†‡	2.1±1.5	2.3±1.6
Initial sodium concentration, mmol/L†	134±6	134±3
No. (%) of patients with seizures before admission	1 (3)	2 (6)
No. (%) of patients who had previously taken oral antibiotics	7 (24)	14 (45)
Etiologic agents, No. of patients (% of β-lactamase–positive strains)		
Haemophilus influenzae type b	20 (40)	25 (20)
Streptococcus pneumoniae	6	3
Neisseria meningitidis	2	2
No isolate	0	0

*There were no statistically significant differences between the two treatment groups.
†Values are mean ± SD.
‡Score devised by Herson and Todd[6] for patients with *H influenzae* type b meningitis.

RESULTS

Study Population

Sixty-one patients were initially enrolled in the study from August 1987 through May 1988. One patient in the placebo group was excluded from the analysis because he was clinically brain-dead on the second day of hospitalization and died 4 days after his admission when ventilatory support was discontinued. There were 60 evaluable patients. Thirty-one patients received cefuroxime and dexamethasone, and 29 received cefuroxime and placebo. The clinical[6] and demographic characteristics of the patients at the time of admission are shown in Table 1. There were

Table 2.—Clinical Course of Illness During Hospitalization

	Drug Treatment Group	
	Placebo (n=29)	Dexamethasone (n=31)
Days to resolution of fever (<38°C)*	3.2±3.3	1.1±0.6†
Total days of fever*	4.4±4.0	2.2±2.1‡
Secondary fever, No. (%) of patients	14 (48)	14 (48)
Seizures, No. (%) of patients	7 (24)	4 (13)
Ataxia, No. (%) of patients	6 (21)	6 (19)
Hemiparesis, No. (%) of patients	3 (10)	0
Hydrocephalus, No. (%) of patients	1 (3)	0
Reactive arthritis, No. (%) of patients	2 (7)	1 (3)
Sterile cerebrospinal fluid at 24 h, No. (%) of patients	24/28 (86)	26/31 (84)

*Values are mean ± SD.
†$P<.001$ by Mann-Whitney U test.
‡$P<.01$ by Mann-Whitney U test.

Table 3.—Changes in CSF and Blood Values Obtained on Admission and 24 Hours After Start of Therapy*

	Difference Between Measurement at Admission and Measurement at 24 h by Drug Treatment Group		
Measurement	Placebo (n=29)	Dexamethasone (n=31)	P†
CSF white blood cell count, $\times 10^6$/L	−862±13 099	+286±6460	NS
CSF protein concentration, g/L	−0.32±0.92	−0.48±1.06	NS
CSF glucose concentration, mmol/L	+0.89±1.09	+1.94±1.50	.005
Blood glucose concentration, mmol/L	−1.99±2.59	−0.41±3.33	.004
CSF/blood glucose ratio	+0.22±0.14	+0.32±0.28	NS

*CSF indicates cerebrospinal fluid. All values are mean ± SD.
†Mann-Whitney U test. NS indicates not significant ($P>.05$).

Table 4.—Magnetic Resonance Imaging Findings

	No. (%) of Patients by Drug Treatment Group	
Finding	Placebo (n=28)	Dexamethasone (n=31)
Normal*	24 (86)	28 (90)
Subdural fluid collection	2 (7)	3 (11)
Focal increased signal	2 (7)	0
Hydrocephalus and infarcts	1 (4)	0
Sinusitis†	9 (32)	12 (39)

*Excludes findings in sinuses.
†Opacification of mastoid and/or maxillary sinuses.

no statistically significant differences between the two treatment groups in any of the listed characteristics.

Clinical Course During Hospitalization

The resolution of clinical signs of meningitis was similar for both treatment groups, with the exception that the patients who received dexamethasone became afebrile significantly more rapidly and had fewer total days of fever than did those who received placebo (Table 2). Fewer patients in the dexamethasone group had evidence of arthritis during the time of hospitalization, but this did not achieve statistical significance. The duration of hospitalization and the incidence of complications was similar for both treatment groups (Table 2). There were no adverse effects of dexamethasone therapy observed, including evidence of gastrointestinal bleeding.

CSF Examination

On repeated CSF culture after approximately 24 hours of therapy, 14% and 16% of cultures to which cephalosporinase was added were still positive in the placebo and dexamethasone treatment groups, respectively. In each case, *H influenzae* type b was the pathogen recovered from the second culture. In these patients, a third CSF culture obtained at approximately 48 hours of therapy was sterile, and relapse did not occur in any patient after the completion of antibiotic therapy. All isolates were susceptible in vitro to cefuroxime. At the beginning of therapy there were no differences between CSF inflammatory indexes (white blood cell count, protein and glucose concentrations) for the two treatment groups. On repeated CSF examination, patients who received dexamethasone had a significantly larger increase in CSF glucose concentration than did those who received placebo (Table 3). At the time of admission, all patients had an elevated blood glucose concentration (7.1±2.2 vs 6.9±3.1 mmol/L for the placebo and dexamethasone groups, respectively), but the decrease in blood glucose concentration after 24 hours of therapy was larger in those who received placebo than in those given dexamethasone (−1.99±2.59 vs −0.41±3.33 mmol/L, $P=.004$). However, the changes in blood glucose concentration could not alone account for the larger increase in CSF glucose concentration in the dexamethasone treatment group.

MRI

Fifty-two patients (88.1%) had a normal MRI (Table 4), as evidenced by normal ventricular size and configuration, normal signal intensity within the brain parenchyma, and the absence of extra-axial fluid collections. Parietal or bifrontal extra-axial fluid collections were seen in five patients (8.5%). Two patients (3.4%) had areas of abnormal in-

tensity within the brain on T_2-weighted images, consisting of focal areas of hyperintense signal in the cerebral hemispheres caused by focal areas of cerebritis, interstitial edema, or infarction. One patient had communicating hydrocephalus at presentation. A repeated MRI done 8 days later for that patient showed diffuse cerebral edema that progressed over 5 weeks to cystic encephalomalacia involving a large portion of the cerebral hemispheres. Twenty-two patients (36%) had either mucoperiosteal thickening or fluid within the mastoid and/or maxillary sinuses on MRI. Abnormal findings on MRI were not associated with clinical signs that would have prompted a radiologic examination of the central nervous system, and the clinical treatment of the patients was not altered as a result of the MRI findings. Furthermore, there were no correlations between MRI findings and the results of audiometric evaluations and 6-week follow-up examinations. There were no complications related either to patient sedation or to MRI.

Six patients had cranial CT scans performed for clinical reasons during hospitalization. Two patients had a normal CT scan; the MRI was normal in one and showed bilateral subdural effusions in the other. Two patients had subdural fluid collections observed on both MRI and CT scan. One patient had cerebral edema on CT scan and a normal MRI. One patient had hydrocephalus and cerebral edema on CT scan while the initial MRI showed hydrocephalus.

Brain Water Content Evaluation

There were no statistically significant differences in the indexes obtained in patients who had received dexamethasone or placebo for either the frontal or parietal gray-matter or white-matter areas (Figs 1 and 2). There was no correlation between the indexes and duration of illness or the number of days the patient had received therapy before MRI evaluation. There was a statistically significant inverse correlation between the patient's age and the indexes for frontal white matter ($r = -.712$, $P < .001$), for parietal white matter ($r = -.467$, $P < .001$), and parietal gray matter ($r = -0.412$, $P = .002$), as assessed by T_1-weighted calculations. Similar correlations were found between age and the T_2-weighted values as well as between age and hydrogen density.

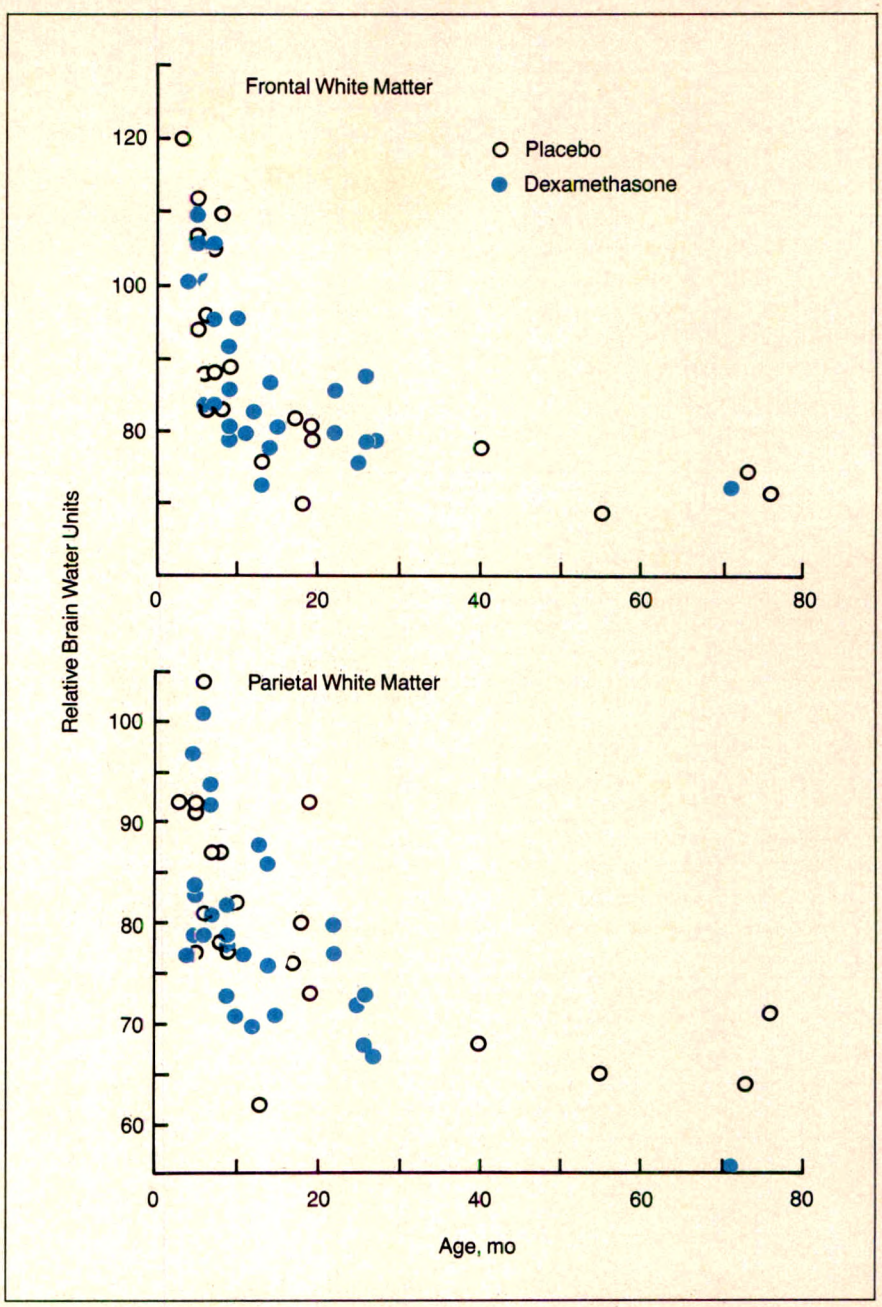


Fig 1.—T_2 relaxation time (in milliseconds) for white matter according to age.

Follow-up Examinations

Fifty-four patients were evaluated 6 weeks after discharge from the hospital. There were no significant differences in neurologic abnormalities (hemiparesis, cranial nerve palsy, ataxia, speech impairment, developmental impairment) for the patients treated with placebo (5/26 [19%]) and dexamethasone (4/28 [14%]).

Fifty-nine patients had audiometric evaluations, and 9 patients had repeated examinations because results of the initial tests were abnormal. Five (17.2%) of 29 in the placebo group and 3 (10%) of 30 in the dexamethasone group had unilateral or bilateral moderate or greater hearing impairment. Seven percent (2/29) and 3% (1/30) had bilateral moderate or greater hearing impair-

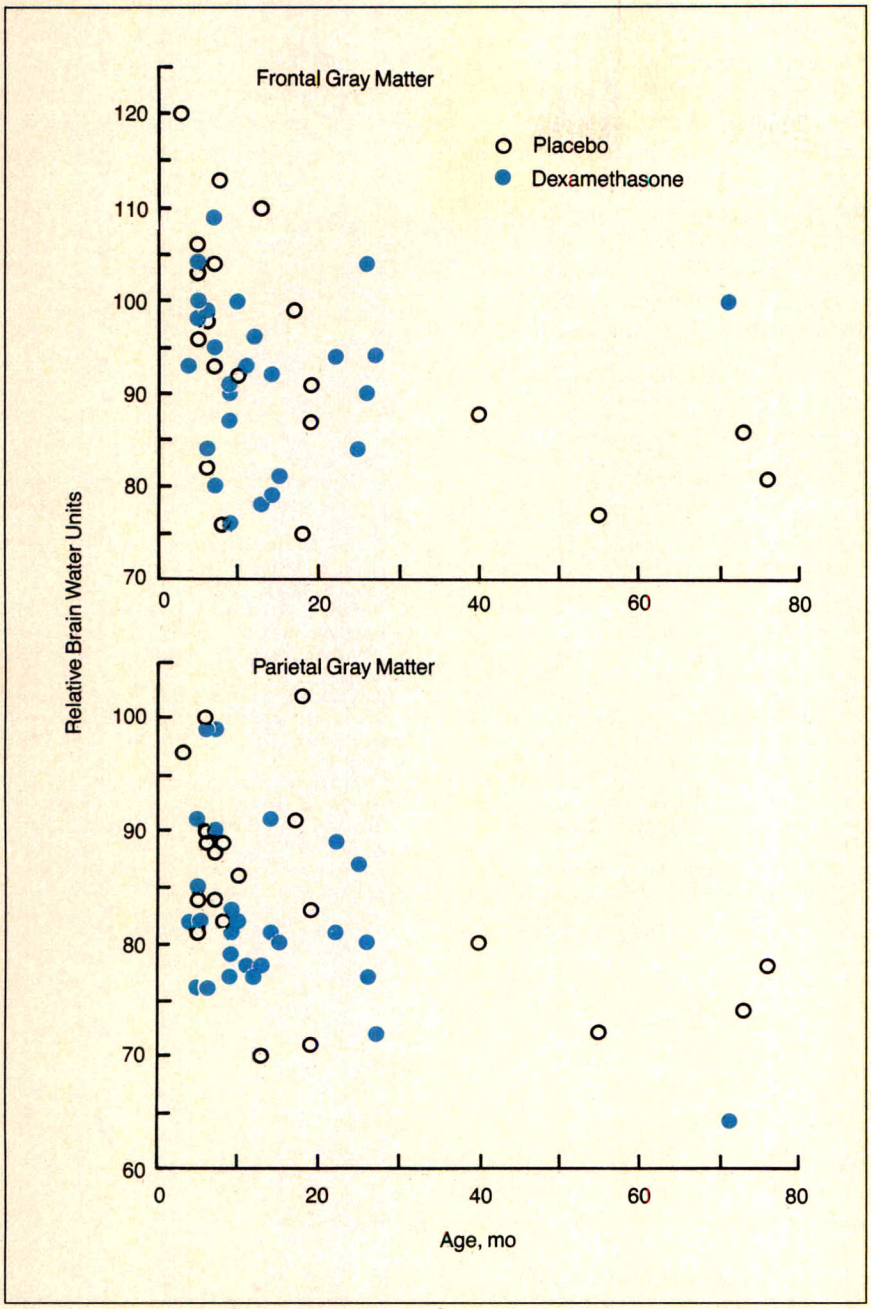


Fig 2.—T_2 relaxation times (in milliseconds) for gray matter according to age.

ment in the placebo and dexamethasone treatment groups, respectively. These differences were not statistically significant.

COMMENT

The CSF findings and clinical course of the dexamethasone-treated patients in this study substantiate the beneficial effects of steroid treatment observed previously.[4] Dexamethasone increased CSF glucose and decreased CSF protein concentrations and shortened the total number of days of fever. There were too few patients enrolled in this study to document adequately the effect of dexamethasone on clinical outcome, especially on hearing. The percentage of patients with unilateral or bilateral moderate or greater hearing impairment in this study who received placebo (5/29 [17.2%]) compared with dexamethasone (3/30 [10%]), however, was similar to results when all three studies were combined (21/113 [19%] vs 11/122 [9%], $P = .03$).[7]

In an attempt to delineate how dexamethasone improves outcome from bacterial meningitis in infants and children, we used MRI to detect intracranial complications and to assess indirectly brain water content. Magnetic resonance imaging is a new radiologic technique that is safe and requires no radiation.[8,9] It is noninvasive and has the potential of producing better imaging than other modalities.[10] Magnetic resonance imaging has been used in a small number of patients with meningitis and was considered useful in demonstrating complications arising from the disease.[11,12] On the other hand, some studies have shown a good correlation between spin-echo relaxation time and brain water content from specimens obtained at the time of surgery.[13,14] In that regard, one study utilizing MRI demonstrated indirectly a reduction in brain water content before and after hemodialysis in eight patients.[15]

In our study, we found a significant inverse correlation between the brain water content of the white matter in both the frontal and parietal lobes and patient age. As the infant brain matures, it undergoes myelination of the white matter accompanied by water loss, as the myelin is relatively hydrophobic.[16,17] Because of the variability in the rate of myelination and, therefore, in the amount of brain water, especially in infants younger than 2 years of age, there was a relative scatter of brain water content values in our patients. We were unable to distinguish by MRI between patients who had received dexamethasone and placebo. It is possible that MRI is not sufficiently sensitive to detect very small differences in brain water content or that changes in brain water content were masked by the intrinsic variability in the amount of brain water that exists between infants of a given age. McMenamin and Volpe[18] showed a rapid decrease in intracranial pressure in the first 4 days of therapy in patients treated for meningitis; thus, it is possible that MRI performed on the third day of treatment or later was too late in course of illness to detect differences in water content values of our study patients. These observations are consistent with results in experimental

H influenzae meningitis, where dexamethasone phosphate and ceftriaxone sodium therapy decreased brain water content and CSF pressure more than ceftriaxone therapy alone, but the differences were not statistically significant.[5] Moreover, the effects were observed 9 hours after the initiation of therapy in those animals.

Magnetic resonance imaging was well tolerated and there were no complications in our children with meningitis. The results of MRI did not alter clinical management, and there was no correlation between findings on MRI and patient outcome, with the exception of the infant in whom hydrocephalus and cerebral infarcts developed. Similar experiences have been reported in two studies of cranial CT in bacterial meningitis.[19,20] In all three studies, the neurologic examinations were the most important predictor of an abnormal radiologic examination and of outcome. Neither MRI nor CT scan of the head should be routinely performed to evaluate children with meningitis. The indications for these examinations should be based on abnormal neurologic findings, persistent or focal seizures, or fever that persists for longer than 7 days.

This work was supported in part by a grant from Glaxo Inc, Research Triangle Park, NC.

We thank the pediatric residents at Parkland Memorial Hospital and Children's Medical Center, Dallas, for their invaluable help throughout the study.

References

1. Sande MA, Scheld WM, McCracken GH Jr. Summary of a workshop: pathophysiology of bacterial meningitis—implications for new management strategies. *Pediatr Infect Dis J.* 1987;6:1167-1171.

2. Mustafa MM, Lebel MH, Ramilo O, et al. Detection of interleukin-1β and cachectin in cerebrospinal fluid of infants and children with bacterial meningitis. Presented at the 28th Interscience Conference on Antimicrobial Agents and Chemotherapy; October 25, 1988; Los Angeles, Calif.

3. Kadurugamuwa JL, Hengstler B, Zak O. Effects of antiinflammatory drugs on arachidonic acid metabolites and cerebrospinal fluid proteins during infectious pneumococcal meningitis in rabbits. *Pediatr Infect Dis J.* 1987;6:1153-1154.

4. Lebel MH, Freij BJ, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. *N Engl J Med.* 1988;319:964-971.

5. Syrogiannopoulos GA, Olsen KD, Reisch JS, McCracken GH. Dexamethasone in the treatment of experimental *Haemophilus influenzae* type b meningitis. *J Infect Dis.* 1987;155:213-219.

6. Herson VC, Todd JK. Prediction of morbidity in *Hemophilus influenzae* meningitis. *Pediatrics.* 1977;59:35-39.

7. McCracken GH Jr, Lebel MH. Dexamethasone therapy for bacterial meningitis in infants and children. *AJDC.* 1989;143:287-289.

8. Alfidi RJ, Haaga JR, El-Yousef SJ, et al. Preliminary experimental results in humans and animals with a superconducting, whole-body, nuclear magnetic resonance scanner. *Radiology.* 1982;143:175-181.

9. Palmer S. Nuclear magnetic resonance imaging. *Med J Aust.* 1983;1:252-253.

10. Cohen MD. Clinical utility of magnetic resonance imaging in pediatrics. *AJDC.* 1986;140:947-956.

11. Davidson HD, Steiner RE. Magnetic resonance imaging in infections of the central nervous system. *AJNR.* 1985;6:499-504.

12. Sze G, Zimmerman RD. The magnetic resonance imaging of infections and inflammatory diseases. *Radiol Clin North Am.* 1988;26:839-859.

13. Naruse S, Horikawa Y, Tanaka C, et al. Significance of proton relaxation time measurement in brain edema, cerebral infarction and brain tumors. *Magn Reson Imaging.* 1986;4:293-304.

14. MacDonald HL, Bell BA, Smith MA, et al. Correlation of human NMR T1 values measured *in vivo* and brain water content. *Br J Radiol.* 1986;59:355-357.

15. Winney RJ, Kean DM, Best JJK. Changes in brain water with haemodialysis. *Lancet.* 1986; 2:1107-1108.

16. Holland BA, Haas DK, Norman D, Brant-Zawadzki M, Newton TH. MRI of normal brain maturation. *AJNR.* 1986;7:201-208.

17. Dietrich RB, Bradley WG, Zaragoza EJ. MR evaluations of early myelination patterns in normal and developmentally delayed infants. *AJR.* 1988; 150:889-896.

18. McMenamin JB, Volpe JJ. Bacterial meningitis in infancy: effects on intracranial pressure and cerebral blood flow velocity. *Neurology.* 1984; 34:500-504.

19. Cabral DA, Flodmark O, Farrell K. Prospective study of computed tomography in acute bacterial meningitis. *J Pediatr.* 1987;111:201-205.

20. Kline MW, Kaplan SL. Computed tomography in bacterial meningitis of childhood. *Pediatr Infect Dis J.* 1988;7:855-857.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Neonatal Adenovirus Pneumonia

William R. Green, MD, A. Wayne Williams, MD (*Arch Pathol Lab Med.* 1989;113:190-191)

Clinical Identification and Comparative Prognosis of High-Risk Patients With *Haemophilus influenzae* Meningitis

Nancy Gary, MS; Nancy Powers, PsyD; James K. Todd, MD

• **One hundred ninety-five consecutive children with *Haemophilus influenzae* meningitis were retrospectively reviewed to identify those patients at high risk of death or severe sequelae using a previously described clinical scoring system. One hundred sixty-nine children (86.7%) had prognostic scores less than or equal to 4.0 and all survived. Twenty-six patients (13.3%) had prognostic scores greater than or equal to 4.5 points. Five of these high-risk patients (2.6% overall) died as a direct result of their acute meningitis. Of the remaining 21 survivors, 15 were available for prospective, observer-blinded, follow-up evaluation, as compared with 15 low-risk control patients matched for age, sex, and year of admission. High-risk patients were significantly more likely to have more serious sequelae (2.0 ± 2.1) as compared with low-risk controls (0.5 ± 0.7). Those high-risk patients who by the choice of their treating physicians had received corticosteroids (and usually osmotic therapy as well) appeared to have outcomes similar to their matched low-risk controls and significantly better than those high-risk patients who did not receive such additional therapy.**

(*AJDC*.1989;143:307-311)

Specific antimicrobial therapy for *Haemophilus influenzae* meningitis has substantially reduced its fatality rate such that the great majority of affected children now survive. Nonetheless, many of these survivors may have moderate to severe sequelae that result in lasting handicaps.[1,2] Thus, although antimicrobial therapy is successful in eradicating the infecting organism, it is hypothesized that the resultant inflammatory response and/or direct effects of residual bacterial products may result in substantial and permanent neurologic damage.[1]

See also pp 287, 290, and 301.

Accepted for publication November 21, 1988.

From The Children's Hospital Kempe Research Center, The Children's Hospital of Denver (Mss Gary and Powers and Dr Todd), Departments of Pediatrics (Ms Gary and Dr Todd) and Microbiology/Immunology (Dr Todd), University of Colorado School of Medicine, Denver.

Reprint requests Children's Hospital, 1056 E 19th Ave, Denver, CO 80218 (Dr Todd).

Experimental studies suggest that corticosteroid therapy may decrease the degree of reactive inflammation and/or cerebral edema in animal models of *Streptococcus pneumoniae* and *H influenzae* meningitis.[3,4] However, past comparative clinical trials of corticosteroid therapy in childhood meningitis have shown equivocal results.[5,6] One problem with these previous studies has been the inclusion of all patients with meningitis in a single comparative group, when only approximately 10% of patients with *H influenzae* meningitis are at risk of dying or developing the severe sequelae used as outcome criteria. In these studies the statistical power was substantially diluted by the inclusion of a large number of patients who were not at risk of developing these complications. Thus, the only methods for truly testing the efficacy of anti-inflammatory therapy for preventing complications of *H influenzae* meningitis would be to treat a very large group of patients and compare them with an untreated control group or to identify at the outset of treatment those patients at high risk of developing complications and treat and analyze them separately in a comparative study.

Herson and Todd[1] have described a scoring system that predicts the risk of either death or severe cortical sequelae but not hearing loss (as estimated by a parent and primary physician questionnaire) associated with *H influenzae* meningitis. We have conducted a comparative blinded evaluation of the clinical outcome of high-risk patients with *H influenzae* meningitis compared with matched low-risk controls to validate further the usefulness of this scoring system, and we present preliminary retrospective data on the possible effects of anti-inflammatory and osmotic therapy in these patients.

PATIENTS AND METHODS

Patients

All patients at The Children's Hospital of Denver (Colo) with *H influenzae* meningitis bacteriologically documented from January 1971 to June 1978 were eligible for this retrospective case selection, prospective outcome evaluation study. These included patients described in the study by Herson and Todd,[1] none of whom had been objectively evaluated for neurologic sequelae. All patient charts were reviewed to document the diagnosis of *H influenzae* meningitis, which required the presence of neurologic symptoms, cerebrospinal fluid pleocytosis, and the isolation of *H influenzae* from either spinal fluid or blood. For inclusion in the study all patients required clinically appropriate antimicrobial therapy based on laboratory susceptibility tests.

Scoring System

Records were reviewed for the following elements of the previously described weighted scoring system: age; duration of illness before diagnosis; presence of seizures (major, motor, or generalized), coma (apnea, nonreactive pupils, no response to pain), shock (systolic blood pressure <60 mm Hg) or hypothermia (temperature <36.6°C); and clinical laboratory abnormalities at the time of admission, including hemoglobin concentration, cerebrospinal fluid white blood cell count, and cerebrospinal fluid glucose (Table 1).[1] Any factor not specifically documented in the patient record was considered to be absent. All patients with a cumulative score of 4.5 or greater were placed in the high-risk study group and those with scores of 4.0 or less were considered to be at low risk based on the previously reported scoring system.

Controls

For each high-risk patient a single low-risk matched control was selected using matching

Table 1.—Scoring System for Prediction of Morbidity in *Haemophilus influenzae* Meningitis*

Factor at Admission*	Points
Severe coma (apnea, nonreactive pupils, no response to pain)	3
Hypothermia (temperature <36.6°C)	2
Seizures (major motor or generalized)	2
Shock (systolic blood pressure <60 mm Hg)	1
Age <12 mo	1
CSF white blood cell count $<1000 \times 10^6$/L	1
Hemoglobin <110 g/L	1
CSF glucose <1.1 mmol/L	0.5
Symptoms persisting >3 d	0.5

*CSF indicates cerebrospinal fluid. Data are from Herson and Todd.[1]

Table 2.—Definitions of Abnormality in Prospective Tests Used for Evaluation of Children Recovered From Meningitis

Outcome Category	Test (Age)	Definition of Abnormal Result
Socioeconomic scale	2-factor index of social position[13]	Numerical scale
Developmental testing		
Cognitive	Bayley Scale of Infant Development[10] (0-30 mo)	Score <80
	McCarthy Scale of Children's Abilities[11] (≥31 mo)	Score <80
Motor	Bayley Scale of Infant Development[10] (0-30 mo)	Score <80
	McCarthy Scale of Children's Abilities[11] (Motor Subscale) (≥31 mo)	Score <39
Clinical	History	Low functional level*
	Physical examination	Institutionalization
	Neurological examination	Cranial nerve defects
Speech	Denver Articulation Screening Examination	Below age-related norm
Hearing	Audiometry	>25-dB threshold per frequency per ear and/or total score >300 dB
Vision	Allen Picture Card Test[7]; Snellen Test[8]	Test failure

*Unable to feed oneself, not independently mobile, cannot communicate, lack of protective response, unable to attend school.

criteria that included age (±3 months), same sex, and date of admission (±4 months). Exceptions to any single criterion were only made if no other child was a better match. All of the low-risk matched controls who were selected were available for prospective outcome evaluation.

Therapy Groups

The high-risk patient group was retrospectively divided further into those who received "extra therapy" and those who received none, ie, "standard therapy." The choice to use extra therapy was made by the treating physicians and was unrelated to any influence of the present or any other study. Before review of the medical reocrds it was decided arbitrarily that those patients placed in the extra therapy group should have received at least one dose of corticosteroid greater or equal to 0.2 mg of dexamethasone per kilogram (or its equivalent) and/or mannitol (≥0.5 g/kg per day with at least two doses given). It was decided prospectively that if shock, hypothermia, or coma was present at the time of admission administration of these therapies needed to be initiated within 1 hour to qualify the patient as satisfying the criteria of the extra therapy group. If shock, hypothermia, and coma were not present, these therapies needed to be given within 6 hours of admission.

Outcome Evaluation

Once the high-risk extra therapy and high-risk standard therapy groups and their controls were identified, all surviving patients were contacted and were requested to participate in a prospective, observer-blinded, follow-up evaluation that included the following elements: an interval history; assessment of socioeconomic status; a complete neurologic examination; vision, hearing, and speech screening; and developmental testing (cognitive and motor) based on the age of the child.

Table 2 shows the various evaluations that were performed by examiners who were blinded to the patients' identity and previous treatment history and lists the criteria for abnormal results. A complete history was obtained and a complete physical examination was performed, including a thorough neurologic evaluation. Patients were considered to be abnormal if they had a decreased functional level compared with their expected age (eg, unable to feed oneself, not independently mobile, cannot express oneself, lack of protective response, unable to attend school), if they were institutionalized, if they continued to have seizures, or if they had evidence of cranial nerve defects or long-tract motor signs.

Two different screening tests for vision were performed (the Allen Picture Card Test[7] and the Snellen[8] test) and abnormalities were defined as a failure of one or both tests. Hearing was tested using standard conditioned audiometric techniques and patients were considered to have abnormal hearing if they exceeded a 25-dB threshold per tested frequency per ear or a total threshold per frequency per ear greater than 300 dB. Speech was tested by the Denver Articulation Screening Exam[9] and was considered abnormal if the result was below the age-related percentile derived from the raw score and the age of the child. Developmental status (both cognitive and motor) was evaluated by a battery of tests that were selected based on the age of the child at the time of evaluation. The Bayley test of mental and psychomotor abilities[10] was performed on children less than or equal to 30 months of age, while the McCarthy scales of children's abilities[11] were administered to those children aged 31 months to 8½ years. The Leiter scale,[12] a nonverbal intelligence test, was administered to children who had substantial language or hearing deficits. Cognitive abnormalities were defined as a score of less than 80 on the Bayley, McCarthy, and Leiter scales and motor delays were defined as a score less than 80 on the Bayley scale and less than 39 on the McCarthy Motor Subscale.[11] The Hollingshead numerical scale[13] was used to evaluate socioeconomic status.

Statistical Analysis

Continuous variables are expressed as the mean ± SD. Groups were compared using Student's *t* test for continuous variables and Fisher's Exact Test for proportional data. The probability of a difference was calculated using two-tailed statistics.

RESULTS

From January 1971 to June 1978 there were 195 children with *H influen-*

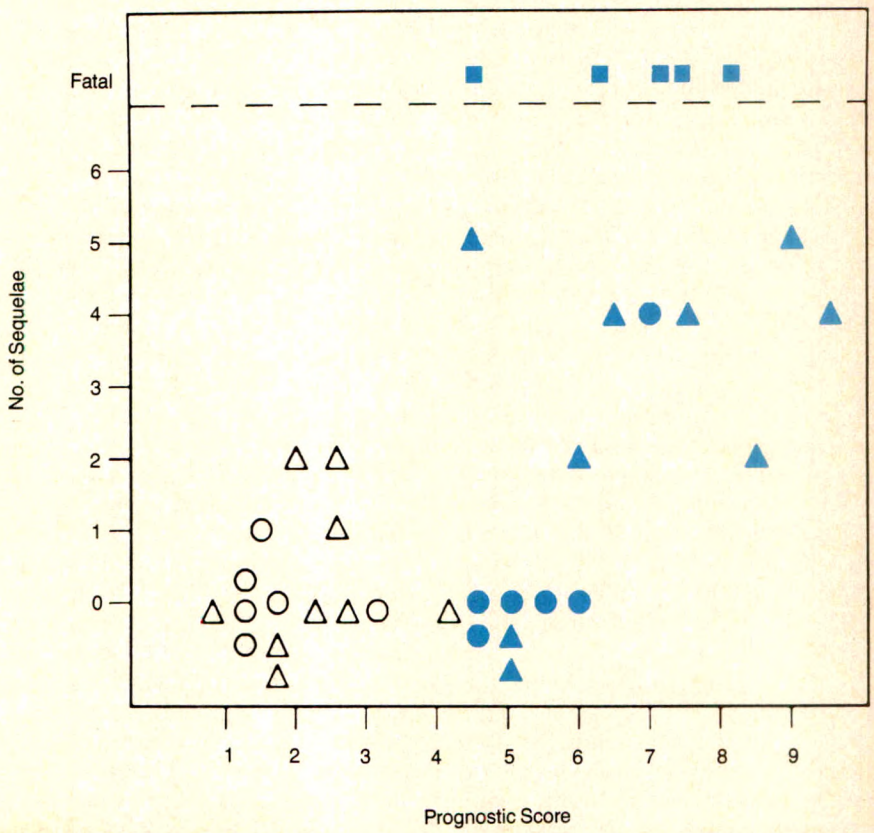
zae meningitis treated at The Children's Hospital of Denver. Twenty-six (13.3%) of these patients had prognostic scores of greater than or equal to 4.5 points and 169 (86.7%) had scores less than or equal to 4.0 points. Five of the 26 children in the high-risk group died as a direct result of their acute meningitis, whereas none of the 169 low-risk patients died, for an overall fatality rate of 2.6%. Of the remaining 21 survivors in the high-risk group, 15 could be contacted and were available for follow-up; 6 had received extra therapy and 9 had not. Of those 6 patients who had received extra therapy, all had received dexamethasone (1.5±0.8 mg/kg per day for 5.7±4.1 days) and 5 also received osmotic agents (mannitol and/or glycerol)(3.0±2.0 g/kg per day for 2.8±1.8 days). None of the low-risk patients available for follow-up had received extra therapy. From these patients appropriate matched controls were selected as described above and were recruited to join the 15 high-risk patients in the prospective outcome evaluation study.

Table 3 shows the comparability of the high-risk patients and their matched controls. There was no significant difference between the high-risk patients and their matched low-risk controls for age, sex, socioeconomic status, antimicrobial therapy, initial serum sodium concentration, initial admission hemoglobin concentration, total amount of intravenous fluids (milliliters per kilogram per day) administered on the first day, or admission date. The high-risk extra therapy group did receive numerically higher volumes of fluid that, because of the small total number of patients, was not statistically significant but could have had an unmeasured influence on the outcome. There were the expected significant ($P<.05$) differences between the high- and low-risk groups for prognostic score and the receipt of anticonvulsants (all 15 of the high-risk patients received anticonvulsants and only 3 of 15 of the low-risk patients did). There were no significant differences between the high-risk extra therapy and high-risk standard therapy groups.

Table 3.—Comparability of Patients With *Haemophilus influenzae* Meningitis in Various Treatment Groups

	High Risk		Low Risk	
	Extra Therapy	Standard Therapy	Extra Control	Standard Control
No. of patients	6	9	6	9
Sex (F)	1	4	1	3
Age, mo				
Onset	3.8±2.6	5.6±2.7	6.5±2.3	7.8±4.2
Evaluation	41.8±15.8	58.9±22.5	43.3±15.7	58.7±22.8
Socioeconomic status	39.7±13.6	42.6±18.4	27.3±21.6	38.3±12.5
Serum sodium, mmol/L	138±12	135±4	136±5	137±4
Intravenous fluid, mL/kg first 24 h	83±30	92±48	130±49	85±43
Anticonvulsants	6†	9‡	1†	2‡
Admission date, y§	76.5±1.6	75.3±1.8	76.7±1.3	75.5±3.5
Prognostic score	5.9±1.6†	6.5±1.8‡	1.8±0.9†	2.2±0.8‡

*Differences between like symbols in each row are significant ($P<.05$) by Fisher's Exact Test.
§Expressed as the mean±SD of the last two digits of the year for each patient.



Outcome of *Haemophilus influenzae* type b meningitis as predicted by prognostic score and influenced by corticosteroid and mannitol therapy. Squares indicate patients who died; solid triangles, high-risk standard therapy group; solid circles, high-risk extra therapy group; open triangles, low-risk standard therapy matched controls; and open circles, low-risk extra therapy matched controls.

The Figure shows the total number of sequelae for each patient, determined as the sum of defects in each of six outcome groups (cognitive, motor, neurologic, speech, hearing, or vision). Patients with a Herson-Todd score of 4.5 points or more were significantly ($P=.002$) more likely to have severe sequelae (2.0±2.1 sequelae) than those patients with a score of 4.0 points or less (0.5±0.7 sequelae). Thus, the high-risk group of patients had a significantly

Table 4.—Number of Sequelae After *Haemophilus influenzae* Meningitis Classified by Treatment Group

Category	No. of Patients With Sequelae*					
	High-Risk			Low-Risk		
	Extra (n=6)	Standard (n=9)	Combined (n=15)	Extra Control (n=6)	Standard Control (n=9)	Combined (n=15)
Cognitive	1†	7†‡	8§	0	0‡	0§
Motor	1†	7†‡	8§	0	1‡	1§
Neurological	1	4	5†	0	0	0†
Speech	1	5	6	0	1	1
Hearing	0	1	1	1	2	3
Vision (No. testable)	0 (5)	2 (8)	3 (13)	0 (5)	1 (8)	1 (13)

*Differences between like symbols in each row are significant ($P<.05$) by Fisher's Exact Test.

worse overall outcome in terms of either death or sequelae than those in the combined low-risk matched group.

Table 4 shows the specific sequelae identified in each study group. There were significant ($P<.05$) differences between the total high-risk group and the total low-risk group for cognitive function, motor function, and neurologic function outcome. The high-risk extra therapy group had a significantly ($P<.05$) better outcome than the high-risk standard therapy group for cognitive and motor function; and a higher proportion of the high-risk standard therapy patients had neurologic and speech abnormalities, although these differences did not reach statistical significance. There were no significant outcome differences between the high-risk extra therapy group and its matched low-risk control group. However, there were significant ($P<.05$) differences for cognitive and motor outcome for the high-risk standard therapy group vs its low-risk control group.

COMMENT

The present study objectively confirms the ability of a previously reported clinical scoring system to predict death and/or severe sequelae in patients with *H influenzae* meningitis. Such a capability is necessary if prospective therapeutic trials to prevent cortical sequelae in high risk patients are to be effectively conducted. It should be emphasized that this scoring system does not predict hearing outcome.

Recent animal model studies have suggested that the use of corticosteroid therapy in experimental meningitis may decrease meningeal inflammation and brain swelling[3,4] but also can reduce the penetration of antibiotics into the cerebrospinal fluid.[14] Brady et al[15] reported several cases of persistent pneumococcal meningitis treated with antibiotics and corticosteroids; they hypothesized that this persistence was due to decreased penetration of antibiotics into the cerebrospinal fluid. It is also clear that corticosteroid therapy in some acute neurologic conditions (ie, stroke, cerebral malaria) may not be of benefit, or may even be deleterious depending on the pathologic process.[16,17] Thus, there are precedents for both benefit and potential harm in the administration of corticosteroids to children with meningitis, precedents that can only be confirmed or refuted by clinical trial.

Several previous controlled trials of steroid therapy in childhood meningitis have come to conflicting conclusions[5,6]; however, each of these studies evaluated the outcome of combined groups of patients at both high and low risk; such a design is less likely to distinguish true differences with the numbers of patients evaluated. De Lemos and Haggerty[5] evaluated the potential effect of methylprednisolone in a randomized, placebo-controlled group of 117 children with bacterial meningitis treated with appropriate antibiotics. They found no significant differences in long-term neurologic and developmental outcome between the two groups, although the steroid-treated group had a higher incidence of bad prognostic factors (coma, shock). Belsey et al,[6] in a similar study, reported a lower incidence of complications in 43 children with bacterial meningitis treated with dexamethasone compared with 43 children treated with placebo, although there was a disproportionate number of patients with bad prognostic indicators (elevated cerebrospinal fluid glutamic oxaloacetic transaminase level, >3-day delay in initiation of antimicrobial treatment) in the control group. Statistically, even if a total of 200 patients had been evaluated in either study, such a design would have been unable to detect a 50% improvement in sequelae at a probability level of .05, assuming an overall risk of 10%.

Although retrospective in terms of allocation of corticosteroid and osmotic therapy, our prospective blinded outcome evaluation study suggests that those patients in the high-risk prognostic group with *H influenzae* meningitis who received corticosteroids (and usually osmotic therapy as well) were more likely to have a favorable outcome similar to that of their low-risk matched controls than those subjects in the high-risk group who received standard therapy. The two high-risk groups were comparable for all investigated aspects of their acute illness other than the receipt of the corticosteroid and osmotic therapy and anticonvulsants. It is certainly possible that some additional unidentified aspect of patient therapy or selection may have played a role in the differences seen between the high-risk extra therapy group and the high-risk standard therapy group (eg, fluid therapy), or that the small numbers of high-risk patients available for evaluation may have randomly biased the results.

Recently, Lebel et al[18] reported the results of two double-blind randomized studies that compared the clinical and hearing outcomes of children with meningitis treated with appropriate antibiotics and dexamethasone and similar children treated with antibiotics and placebo. Although complex in its design and interpretation, the study showed a significantly lower incidence of moderate or severe hearing loss in the combined study groups that received dexamethasone. Although not significant, given the numbers studied, there was a trend ($P=.07$) toward reduced neurologic abnormalities in the dexametha-

sone groups. There was no significant difference in antibiotic penetration into the cerebrospinal fluid or delay in its sterilization with the antibiotics (ie, cefuroxime, cefatriaxone) used. Two patients in the corticosteroid-treated group had severe gastrointestinal tract bleeding that required transfusion.

Smith,[19] in a related editorial, presented some reservations about these conclusions and made the cautious recommendation that corticosteroids might be useful in a severely ill child with *H influenzae* meningitis, but felt that broader application should await the results of a confirmatory study documenting safety.

Given the encouraging preliminary results reported by Lebel et al[18] and the present study, it is possible that corticosteroids and perhaps other anti-inflammatory or supportive (eg, osmotic agents) therapies may prove to be of benefit in reducing the sequelae of bacterial meningitis in children. It is clear, however, that additional studies with larger numbers of patients or the use of a validated, prognostic scoring system (such as the one reported herein for cortical sequelae) to focus on high-risk patients will be necessary to substantiate these observations further.

We would like to thank Linda Johnson for performing the audiologic evaluations and Donna Shambaugh for manuscript preparation.

References

1. Herson VC, Todd JK. Prediction of morbidity in *Hemophilus influenzae* meningitis. *Pediatrics.* 1977;59:35-39.
2. Sell SHW, Merrill RE, Doyne EO, Zimsky EP. Long-term sequelae of *Haemophilus influenzae* meningitis. *Pediatrics.* 1972;49:206.
3. Nolan CM, McAllister CK, Walters E, Beaty HN. Experimental pneumococcal meningitis: IV. the effect of methylprednisolone on meningeal inflammation. *J Lab Clin Med.* 1978;91:979-988.
4. Syrogiannopoulos G, Olsen KD, Reisch JS, McCracken GH Jr. Dexamethasone in the treatment of experimental *Haemophilus influenzae* type B meningitis. *J Infect Dis.* 1987;155:213-219.
5. De Lemos RA, Haggerty RJ. Corticosteroids as an adjunct to treatment in bacterial meningitis. *Pediatrics.* 1969;44:30-34.
6. Belsey MA, Hoffpauir CW, Smith MHD. Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of results. *Pediatrics.* 1969;44:503-513.
7. Allen HF. A new picture series for preschool vision testing. *Am J Ophthalmol.* 1957;44:38.
8. Snellen H. Cited by Duke-Elder WS. *Textbook of Ophthalmology.* St Louis, Mo: CV Mosby Co; 1940;2:932.
9. Drumwright A, Van Natta P, Camp B, Frankenburg W, Drexler H: The Denver articulation screening exam. *J Speech Hear Disord.* 1973; 38:3-14.
10. Bayley N. *Manual for the Bayley Scale of Infant Development.* New York, NY: The Psychological Corp; 1969.
11. McCarthy D. *McCarthy Scales of Children's Abilities.* New York, NY: The Psychological Corp; 1972.
12. Levine MN, ed. *The Leiter International Performance Scale: A Handbook.* Los Angeles, Calif: Western Psychological Services; 1982.
13. Hollingshead AB. *Two Factor Index of Social Position.* New Haven, Conn: Yale Station; 1965.
14. Sheld WM, Brodeur JP. Effect of methylprednisolone (MP) on antibiotic entry into the cerebrospinal fluid (CSF). *Clin Res.* 1981;29:396A.
15. Brady MT, Kaplan SL, Taber LH. Association between persistence of pneumococcal meningitis and dexamethasone administration. *J Pediatr.* 1981;99:924-926.
16. Warrell DA, Looareesuwan S, Warrell MJ, et al. Dexamethasone proves deleterious in cerebral malaria. a double-blind trial in 100 comatose patients. *N Engl J Med.* 1982;306:313-319.
17. Mulley G, Wilcox RG, Mitchell JRA. Dexamethasone in acute stroke. *Br Med J.* 1978;2: 994-996.
18. Lebel MH, Bishara JF, Syrogiannopoulos GA, et al. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. *N Engl J Med.* 1988;319:965-971.
19. Smith AL. Neurologic sequelae of meningitis. *N Engl J Med.* 1988;319:1012-1013. Editorial.

In Other AMA Journals

JAMA

Evaluation of Potentially Preventable Deaths Among Pedestrian and Bicyclist Fatalities

F. P. Rivara; R. V. Maier; B. A. Mueller; G. A. Luna; B. G. Dicker; C. M. Herman; J. W. Kenagy; M. K. Copass; C. J. Carrico (*JAMA.* 1989;261:566)

Health Care Financing Policy for Hospitalized Pediatric Patients

Eric Munoz, MD, MBA; Donald Chalfin, MD; Jonathan Goldstein, MPA; Rudy Lackner, MD; Katherine Mulloy, AS; Leslie Wise, MD

• Prospective hospital payment systems using the federal Medicare DRG payment model are changing hospital reimbursement. Currently, many states have adopted diagnosis related group (DRG) prospective "all payer systems" using the federal model. All payer systems, whereby Medicaid, Blue Cross, and other commercial insurers pay by the DRG mode, prevent cost shifting between payers. New York state has used an all payer system since Jan 1, 1988. This study simulated DRG all payer methods for a large sample (N = 16 084) of pediatric patients for a three-year period using the New York DRG all payer reimbursement system now in effect. Medicaid pediatric patients had (adjusted for DRG weight index) a longer hospital stay and greater total hospital cost compared with pediatric patients from Blue Cross and other commercial payers. Medicaid pediatric patients also had a greater severity of illness compared with patients from Blue Cross and other payers. Pediatric patients in all payment groups (ie, Medicaid, Blue Cross, and other commercial insurers) generated financial risk under the DRG all payer scheme. Medicaid pediatric patients generated the greatest financial risk, however. These data suggest that state and private payers may be under-reimbursing for the care of the hospitalized pediatric patient using the DRG prospective hospital payment scheme. Health care financing policy for pediatric patients may limit both access and quality of care.

(*AJDC*. 1989;143:312-315)

Accepted for publication Sept 2, 1988.

From the Departments of Surgery (Drs Munoz, Lackner, and Wise, Mr Goldstein, and Ms Mulloy) and Medicine (Dr Chalfin), Long Island Jewish Medical Center, New Hyde Park, NY; and the Departments of Surgery (Drs Munoz and Wise) and Medicine (Dr Chalfin), State University of New York, Stonybrook. Dr Munoz is now Medical Director of the Hospital of Medicine and Dentistry of New Jersey, Newark.

Reprint requests to Research Division, Department of Surgery, Long Island Jewish Medical Center, New Hyde Park, NY 11042 (Dr Munoz).

Hospital reimbursement is undergoing a fundamental change from the cost-plus "public utility model" to the "competitive" risk-generating model.[1] Aggregate health care expenditures in the United States are rising as fast as ever; health care costs for 1987 increased at three times the rate of overall US economic growth.[2] Medicare hospital payment using the diagnosis related group (DRG) prospective payment system (PPS) has been phased in for the federal payment portion of 6000 American hospitals from 1983 through 1986.[3] Aggregate increases in Medicare expenditures per case during the first three years of the PPS were 10.0% for the first year and 10.4% for the second year but only 6.2% for the third year.[4] Simultaneously, a number of hospital payers have begun to use the federal Medicare DRG model to reimburse for other adult and pediatric patients by a "per-case" method.

For editorial comment see p 292.

Although there has been some control for federal hospital expenditures, Medicare physician expenditures (ie, part B Medicare) have grown substantially during the early years of DRGs. For the third year of the Medicare hospital DRG PPS, for example, part B Medicare expenditures grew at an astounding 33.4% rate (oral communication, Office of Statistics and Data Management, Bureau of Data Management and Strategy, Baltimore, March 1988). There is concern that the providers of care (ie, hospitals and physicians) have been able to continue "demand" for increases in aggregate health care expenditures.[5] The private hospital insurance sector is simultaneously experiencing large increases in aggregate medical care expenditures. Insurance premiums for many employees and certain state and local governments are increasing dramatically (*New York Times*, June 30, 1987, p B4). Physicians contend that much of this increase in aggregate expenditures has been caused by the continued aging of the population, improvements in medical technology and outcome, and the delivery of more services to the patient.[6] Concern has arisen that federal and state governments and private insurers have begun to abandon or "shift" payment for the care of the hospitalized patient. In addition, despite growing amounts of data that suggest there are inequities in the federal DRG system payment model, both the US Congress and the Health Care Financing Administration have resisted any major changes.[7-9]

The federal Medicare DRG classification system has become the national model for prospective payment of patients who require hospital care. Currently, one third of the states are using DRG "all payer systems," whereby all payers (ie, Medicare, Medicaid, Blue Cross, and other commercial insurers) are using DRG prospective hospital payment.[10] All payer systems are thought to prevent or retard "cost shifting" between payers. Hospitals face increasing economic risk, however, as per-case DRG prospective methods of payment become predominant. The purposes of this study were to analyze the resource characteristics by payer for a large group of hospitalized pediatric patients and to analyze the financial effects of a DRG prospective all payer system vis-à-vis these patients.

METHODS

The Long Island Jewish Medical Center, New Hyde Park, NY, is an 805-bed academic

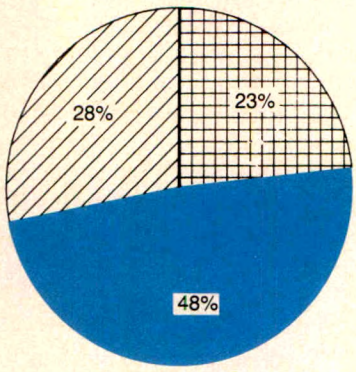


Fig 1.—Aggregate hospital costs for pediatric patients by payer. Greatest percentage of total pediatric hospital costs at our hospital was for Blue Cross patients (solid wedge), followed by patients with other commercial insurers (diagonally hatched wedge) and Medicaid (cross-hatched wedge). Mix may vary by hospital ownership, mission, size, and geographic location.

Table 1.—Resource Characteristics by Payer*

Type of Insurance	No. of Patients	DRG Weight Index	Length of Stay in Hospital, d	Total Hospital Cost, $	No. of Diagnosis Codes	No. of Procedure Codes
Before Correction for DRG Weight Index						
Blue Cross	8449	1.0130†	7.3‡	5848‡	1.87†	1.08†
Medicaid	2724	1.0402	11.8†	8727†	2.32†	1.12
Commercial insurers	4911	1.1268†	6.8†	5870‡	1.93	1.20†
All patients	16084	1.0524	7.9	6342	1.96	1.12
After Correction for DRG Weight Index						
Blue Cross	8449	. . .	7.4‡	5963‡	2.54‡	1.37
Medicaid	2724	. . .	11.3†	8227†	3.03†	1.41
Commercial insurers	4911	. . .	6.8†	5698†	2.49†	1.33
All patients	16084	. . .	7.9	6266	2.61	1.37

*All values are mean values. DRG indicates diagnosis related group.
†$P<.01$ compared with value for all patients.
‡$P<.05$ compared with value for all patients.

medical center located in suburban New York with a 155-bed pediatric hospital. We analyzed all pediatric patients (patients 0 through 18 years of age [N = 16 084]) admitted from Jan 1, 1985, through Dec 31, 1987. We *simulated* a DRG all payer system in constant dollars by using the New York state all payer DRG methodology for Medicaid, Blue Cross, commercial insurers, and other payers. Medicare patients were not studied since there were only five Medicare pediatric admissions during the study period. The DRG payments by non-Medicare payers were *deflated* by the hospital market basket adjustment (4.1% for 1985, 3.1% for 1986, and 3.5% for 1987) for the simulated "real" DRG reimbursement for fiscal 1985 and 1986. We used our clinical financial database to *simulate* a typical DRG all payer system (New York state began using an all payer system on Jan 1, 1988) in constant dollars for one large academic medical center. The federal and state DRG methodology for both inlier and outlier payment (for both the cost and length of stay) was used. The Long Island Jewish Medical Center is categorized as an urban teaching hospital by the DRG reimbursement scheme. There were pediatric patients in 389 of the 477 DRGs; 1365 patients paid for themselves or did not pay.

The hospital cost per patient was computed using patient-specific charge data and our hospital's cost-to-charge ratio. This was the most accurate costing methodology in effect at our hospital at the time of the study. A number of factors were recorded for each patient, including the following: age, total hospital cost, hospital length of stay in days, DRG weight index, profit or loss under DRG reimbursement, number of ICD-9-CM diagnosis codes, number of ICD-9-CM procedure codes, total number of ICD-9-CM codes (as a proxy for severity of illness), percentage of outliers, and mortality. In addition, certain clinical variables were measured, such as intensive care unit or emergency department admission or the need for a blood transfusion. The analysis of variance test was used to test for statistical significance between groups of patients.

The hospital cost per patient was obtained by utilizing per-patient charge-specific data and converting these charges to hospital costs. Cost-to-charge ratios utilized by our hospital accounting division were used to convert charges to costs. The ratios were developed by our Medicare cost accounting division and use a step-down allocative method to develop measures of expense. The following ratios were used for each hospital service category.

Category	Ratio
Room and board	0.75
Latoratory	0.40
Blood (storage, processing, transfusion, and products)	1.15
Pathology	2.42
Diagnostic radiology	0.94
Therapeutic radiology	1.71
Operating room	1.10
Recovery room	1.15
Respiratory therapy	0.76
Electrocardiology	0.25
Electroencephalography	1.40
Medical supplies	1.00
Pharmacy	1.00
Diagnostic ultrasound	0.46
Computed tomography	0.53
Emergency department	0.91
Pulmonary function	0.08

Thus, to obtain the hospital cost for a room and board charge of $100, the following calculation was performed: $\$100 \times 0.75 = \$75$; laboratory, $\$100 \times 0.40 = \$40$; pathology, $\$100 \times 2.42 = \$242$; and so on. However, costing methodologies in general are only *modestly accurate* at assessing the *true cost* for each hospitalized patient.

RESULTS

The total hospital costs for the 16 084 pediatric patients during the study period were $102 010 804. Pediatric patients covered by Blue Cross accounted for the greatest percentage of total hospital costs, followed by other commercial insurers and Medicaid (Fig 1). The mean DRG weight index per pediatric patient for all patients was 1.0524; the highest DRG weight index per pediatric patient was for commercial insurance patients, 1.1268 (Table 1). The mean hospital length of stay per pediatric patient for all patients was 7.9 days. The longest hospital length of stay per pediatric patient was for Medicaid patients (11.8 days), and the shortest length of stay was for commercial insurance patients (6.8 days). The mean hospital length of stay adjusted for the DRG weight index was highest for Medicaid pediatric patients and lowest for commercial insurance patients (Fig 2). The mean total hospital cost per pediatric patient for all patients was $6342; the mean total hospital cost per patient was highest for Medicaid patients, $8727. The mean total hospital cost adjusted for the DRG weight index was highest for Medicaid pediatric patients (Fig 3). The mean number of ICD-9-CM diagno-

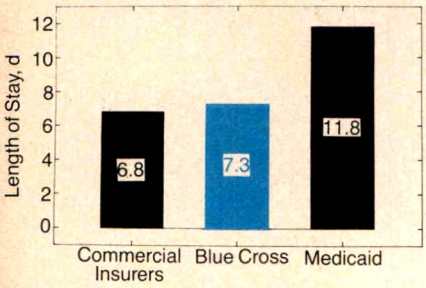


Fig 2.—Hospital length of stay per pediatric patient (adjusted for diagnosis related group weight index) by payer. Longest stay was for Medicaid patients.

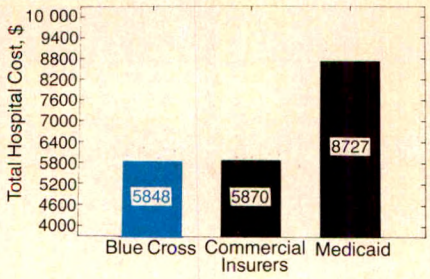


Fig 3.—Total hospital costs per pediatric patient (adjusted for diagnosis related group weight index) by payer. Cost was highest for Medicaid patients.

Table 2.—Clinical Characteristics and Financial Position by Payer*

Characteristic	Blue Cross	Medicaid	Commercial Insurers	All Patients
Age, y	7.3†	6.6†	7.0	7.1
Profit or (loss), $	(2198)	(4696)†	(1264)†	(2336)
No. of ICD-9-CM codes	2.95†	3.44†	3.14	3.09
Intensive care unit admission, %	9.2†	11.0	13.1†	10.7
Emergency department admission, %	30.6†	26.1†	31.2	30.0
Need for blood transfusion, %	8.0†	9.7	11.0†	9.2
Mortality rate, %	0.5‡	1.1	1.2‡	0.8

*All values are mean values.
†$P<.01$ compared with value for all patients.
‡$P<.05$ compared with value for all patients.

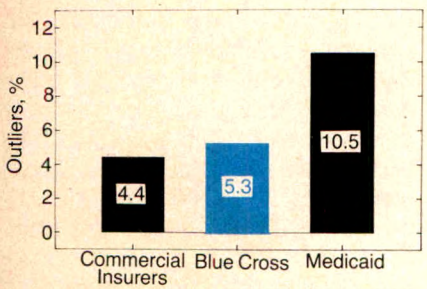


Fig 4.—Percentage of outliers among pediatric patients by payer. Percentage was highest for Medicaid patients and lowest for other commercial insurers.

sis codes per patient for all patients was highest for Medicaid patients (2.32 codes per patient); when adjusted for the DRG weight index it was highest for Medicaid patients (3.03 codes per patient). The mean number of ICD-9-CM procedure codes per pediatric patient for all patients was 1.12. Commercial insurance patients had the greatest number of procedure codes (1.20 codes per patient); Medicaid had the greatest number of procedure codes per patient adjusted for the DRG weight index, 1.41 codes.

The mean age per pediatric patient for all patients was 7.0 years; Blue Cross patients were the oldest (7.3 years, Table 2). The DRG *simulated payment* using New York state all payer DRG payment rates for Medicaid, Blue Cross, and other commercial payers (deflated to constant dollars for the study period) demonstrated a total loss of $37 571 663 for the three-year period; ie, a $2335 loss per patient. Medicaid pediatric patients generated the greatest *loss per patient*, followed by Blue Cross and then other commercial payers, under DRG prospective hospital payment. The percentage of outliers for all pediatric patients was 5.9%. The percentage of outliers was highest for Medicaid patients and lowest for other commercial payers (Fig 4). The total number of ICD-9-CM codes (as a proxy for severity of illness) was highest for Medicaid patients, 3.44 codes per patient (Table 2). Clinical resource utilization as measured by intensive care unit or emergency department admission or the need for a blood transfusion was similar for Medicaid patients, Blue Cross patients, and other commercial insurance patients. The mortality rate for all pediatric patients was 0.8%; the highest mortality rate was for commercial insurance patients.

COMMENT

The federal Medicare DRG system has been on-line for five years, with a mixed review regarding its effectiveness.[3] Hospitals contend they have been underpaid by DRGs and that many hospitals are approaching financial ruin.[11] Studies of the effect of the Medicare DRG program indicate that there has been no major impact (ie, positive or negative) of DRGs on American health care and clinical research, technology diffusion, access, or quality of care.[4] The federal DRG program is thus being used as a model to bring other payers on-line vis-à-vis DRG prospective payment.

We analyzed hospital resource consumption by payers for a large group of pediatric patients. About one fourth of our total hospital costs for these patients were generated by Medicaid patients. Medicaid pediatric patients had a longer length of stay and a greater total hospital cost after adjustment for the DRG weight index compared with pediatric patients covered by Blue Cross and other commercial payers. Medicaid pediatric patients had a greater proportion of outliers (ie, very expensive patients). Medicaid pediatric patients also appeared more severely ill compared with patients covered by Blue Cross and other commercial payers. Our analysis was performed *simulating* the current 1988 New York state all payer system using cost data at our hospital from three previous years (ie, 1985, 1986, and 1987) and adjusting the payment by a standard proportion (ie, the hospital market basket). This financial analysis suggests that DRG prospective payment all payer systems may *under-reimburse* the state and privately funded portions for the care of the hospitalized pediatric patient. This raises a question regarding the equity of DRG all payer payment for the care of the hospitalized pediatric patient. It also raises a serious question regarding the equity of the

"public" portion of DRG payment, at least at our large teaching hospital.

Previously, the "reasonable costs" for the hospital care of each patient were reimbursed. Medicare was the first to switch to a DRG prospective hospital payment system for the 10 million annual Medicare patients requiring hospitalization. Financial data for the first three years of the Medicare PPS indicate that the revenue-per-case increases for Medicare are slowing. State Medicaid expenditures have been severely strained in the last few years. Aggregate data suggest that Medicaid benefits are being curtailed and that Medicaid expenditures are decreasing relative to other hospital payers. Concurrently, private health insurers (ie, Blue Cross and other commercial insurers) appear to be experiencing cost increases for the care of the hospitalized patient. The major portion of this private insurance fund is borne by both industry and the consumer. Health care financing for the care of the hospitalized pediatric patient may be being curtailed (as demonstrated using our historical data). Although no optimum relative level of Medicaid and private insurance expenditures for pediatric patients exists a priori, policymakers appear to be promising the patient more health care services while refusing to pay adequately for them. It may also be possible to subsidize less profitable patients or services from more profitable patients or services; this will be more difficult in the future.

American medicine is entering a very challenging era. Politicians are promising the general public "comprehensive cost-effective medical care for all." It appears that health care financing policy will drive health care public policy for the field of pediatrics. The political forces instituting health policy, however, seem to find it impossible to "explicitly" state that medical benefits are being curtailed or that hospital costs are being shifted. As studies such as this one suggest, health care pediatric financing policy for payers may be driving *relative decreases* in expenditures for hospital care. This affects both the equity of and access to pediatric services. Policymakers have renamed this reduction in payment for pediatric hospital services, using terms such as *prudent buyer* of health services, improvements in efficiency, and the like. Our study demonstrated, however, that our all payer DRG plan underpays for the care of the hospitalized pediatric patient at our large teaching hospital. This type of health care financing policy, if allowed to continue, will ultimately lead to *a decrease* in both access and the quality of care for pediatric patients. Pediatricians must begin to seriously study the questions related to health care policy, management, and finance and must advocate equitable hospital reimbursement for all pediatric patients.

This study analyzed the equity of DRG prospective all payer reimbursement for pediatric patients at a large teaching hospital. Analysis of 16 084 pediatric patients *simulated* (in constant dollars) the current New York state all payer system in effect for patients with Medicaid, Blue Cross, and other commercial insurance using hospital cost and reimbursement data from three previous years. Medicaid pediatric patients had (on average) greater hospital resource utilization and a greater severity of illness compared with pediatric patients covered by Blue Cross and other commercial insurance payers. Pediatric patients covered by all payers, however, generated losses to the hospital under our current DRG hospital all payer system. These data suggest that the state and private hospital financing DRG system may be under-reimbursing for the care of the hospitalized pediatric patient using the DRG classification system. Health care financing policy for pediatric patients may affect both access and the quality of care for these patients.

We thank James Moyer and Gordon Doletto of the Divisions of Management Information Systems and the Diagnosis Related Group Task Force of the Long Island Jewish Medical Center, New Hyde Park, NY. We also thank Christina Weiss for preparation of this manuscript.

References

1. Igelhart JD: Medicare begins prospective payment for hospitals. *N Engl J Med* 1983; 308:1428-1432.
2. *1986-1987 Source Book on Health Insurance Data*. Washington, DC, Health Insurance Association of America, 1987.
3. Schramm CJ, Gabel J: Sounding board: Prospective payment: Some retrospective observations. *N Engl J Med* 1988;318:1681-1683.
4. Prospective Payment Assessment Commission: *Medicare Prospective Payment and the American Health Care System*, report to Congress, June 1988.
5. Office of Technology Assessment: *Medicare's Prospective Payment System*. New York, Springer Publishing Co Inc, 1986.
6. Schwartz WG: The inevitable failure of current cost-containment strategies. *JAMA* 1987; 257:220-224.
7. Munoz E, Sterman H, Cohen JR, et al: Financial risk, hospital cost, complications and comorbidities (CCs) in surgical non-CC stratified DRGs. *Ann Surg* 1988;207:305-309.
8. Jencks SF, Dobson A: Refining case-mix adjustment. *N Engl J Med* 1987;317:679-692.
9. Medicare program: Changes to the inpatient hospital prospective payment system and fiscal year 1989 rates. *Federal Register* 1988;53(May 27):19497-19686.
10. Muñoz E, Soldano R, Gross H, et al: Diagnosis related groups and the transfer of general surgical patients between hospitals. *Arch Surg* 1988;123:68-71.
11. McCarthy CM: DRGs: Five years later. *N Engl J Med* 1988;318:1683-1686.

In Other AMA Journals

JAMA

International Congress on Peer Review in Biomedical Publications

D. Rennie; E. Knoll; A. Flanagin (*JAMA*. 1989;261:749)

Respiratory Syncytial Virus Outbreak on American Samoa

Evaluation of Risk Factors

Edward B. Hayes, MD; Eugene S. Hurwitz, MD;
Lawrence B. Schonberger, MD; Larry J. Anderson, MD

• Acute respiratory illness is one of the leading causes of childhood mortality in developing nations. We investigated an increase in hospitalizations of children less than 2 years old for severe lower respiratory tract illness (LRI) from October 1986 through December 1986 on the island of American Samoa. Hospitalization rates were highest in children less than 6 months of age (60 of 1000 compared with 22 of 1000 for those 6 to 11 months of age, and seven of 1000 for those 12 to 24 months of age). The outbreak was more severe than in previous years, with ten (19%) of 54 patients admitted to the intensive care unit (ICU) compared with three (7%) of 42 and one (3%) of 40 during the same months of 1985 and 1984. Two patients died. Most patients had clinical bronchiolitis; of 34 patients tested, serologic or nasal aspirate evidence of recent respiratory syncytial virus (RSV) infection was found in 18 (53%). A study of patients younger than 1 year of age demonstrated that patients hospitalized with LRI were more likely to have a household member who smoked cigarettes (18/20, 90%) than outpatient controls without recent respiratory illness (8/15, 53%). Maternal sera obtained between December 1985 and October 1986 showed no protective effect of either detectable IgG or neutralizing antibody to two major groups of RSV. Our study documents the involvement of RSV in an outbreak of severe LRI among infants in a tropical area and further suggests that exposure to cigarette smoke is a risk factor for LRI in infants.

(*AJDC* 1989;143:316-321)

Accepted for publication Nov 9, 1988.

From the Division of Viral Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta.

Reprint requests to Centers for Disease Control, San Juan Laboratories, GPO Box 4532, San Juan, Puerto Rico 00936 (Dr Hayes).

Acute respiratory infections (ARI) are a leading cause of childhood mortality worldwide, annually resulting in the death of an estimated 4 million children less than 5 years old.[1] This is approximately 27% of the total annual childhood deaths in this age group worldwide.[1] An international effort is under way to reduce mortality from ARI.[2] The epidemiologic conditions of ARI in developing areas remain poorly defined, however, with important gaps in knowledge of the cause, immunology, and risk factors of these illnesses. Better understanding of the cause and epidemiologic conditions of ARI, particularly in developing and tropical areas, is important to determine effective intervention strategies, including use of viral and bacterial vaccines and antimicrobial drugs.

Bronchiolitis is a major component of childhood ARI, and respiratory syncytial virus (RSV) is the single most important cause of bronchiolitis as well as an important contributor to childhood pneumonia.[3-5] Both bronchiolitis and RSV infection tend to occur most frequently in children less than 2 years old.[3,6]

From October through December 1986 an increase in hospital and intensive care unit (ICU) admissions of children less than 2 years old with lower respiratory tract illness (LRI) occurred on Tutuila, the principal island of American Samoa, a group of tropical islands in the South Pacific. Most of these children had clinical bronchiolitis. We investigated this outbreak to further define seasonality, cause, and risk factors associated with LRI in this age group in a tropical area.

PATIENTS AND METHODS

A summary of the study groups is shown in Table 1. Details are described below.

Defining the Outbreak

To define the timing, geography, and characteristics of the outbreak, we first reviewed admission logs at the only hospital on the island and recorded numbers of pediatric hospital and ICU admissions (less than 18 years of age) for LRI by month since September 1983. Primary diagnoses of any form of LRI, such as bronchiolitis, pneumonia, asthma, wheezing pneumonia, or bronchitis, were included. From the record review we confirmed that an increase in admission of patients with LRI occurred during October and November 1986 that was confined to children less than 2 years old. All subsequent analyses were therefore limited to this age group. During the field investigation in American Samoa, Nov 17 through Dec 17, 1986, we reviewed all 45 available charts of the 47 children less than 2 years old admitted with LRI from Oct 1 through Dec 17, 1986, and abstracted clinical, demographic, and geographic data. After our departure, admissions data for the remaining weeks of December were obtained by telephone.

Etiologic Studies

Etiologic studies were performed on 34 of the 47 inpatients less than 2 years old, including eight of the ten patients in the ICU. We attempted to obtain nasal aspirates and acute and convalescent sera from all acutely ill patients during the field investigation period and we attempted to obtain convalescent sera from all patients who had been ill before our arrival. A few acute sera and nasal aspirates had been stored at 0°C by local pediatricians before our arrival and these were also tested. Viral culture was attempted from nasal aspirates taken from 11 acutely ill inpatients. These samples were frozen at either 0°C or in liquid nitrogen and shipped by

air to the Centers for Disease Control Respiratory and Enterovirus Laboratory in Atlanta. Aspirates from 18 acutely ill patients were tested by enzyme-linked immunosorbent assay (ELISA) and/or time-resolved fluoroimmunoassay (TR-FIA) for the presence of RSV and adenovirus antigens. Acute-phase (seven days or less from onset of illness) and convalescent-phase (greater than 14 days from onset) paired sera were obtained from 13 patients, and convalescent sera were only obtained from an additional 21 patients. Serum was tested for RSV-specific IgG and IgM by ELISA.

The 13 available painted sera were tested for hemagglutination inhibition antibodies against adenovirus type 7; parainfluenza types 1, 2, and 3; influenza A/Taiwan/1/86; and influenza B/Ann Arbor/1/86. In addition, six of these pairs were tested for serum neutralizing antibody against echovirus type 13, which was isolated from one patient (there was insufficient sera from the remaining seven patients to test all sera to echovirus, an unlikely candidate for causing epidemic LRI).

Case-Control Study for Risk Factors

To evaluate risk factors for severe LRI, we conducted a case-control study from Dec 4 to Dec 17, 1986. Because children less than 1 year old had the highest attack rate and because they had not been exposed to the previous year's season of LRI, we limited the study to this age group. We were able to contact, interview, and obtain serum samples from 20 of 43 patients less than 1 year old who had been hospitalized between October 1 and December 17 for LRI. Included in this 20 were six of nine infants with LRI who had been admitted to the ICU. To obtain controls we visited well-child and general pediatric clinics at all four public health care facilities located throughout the island. A group of 60 controls with similar ages to patients in the study were selected from infants who presented for well-child care or with a complaint other than LRI during our visits to the clinics. Caretakers of each control were interviewed by standard questionnaire regarding previous respiratory illness in their child. Of 60 controls selected, 45 reported one or more signs or symptoms of respiratory illness (such as fever, cough, otitis, runny nose, or wheezing) that did not require hospitalization between October 1 and December 17, and were classified as ill controls. The remaining 15 reported no respiratory illness during this period and were classified as well controls.

Caretakers of all study subjects were administered a standard questionnaire concerning potential risk factors for severe LRI, such as history of breast-feeding, predisposing cardiorespiratory illness, birth weight, gestational maturity, number of children sleeping in the house, and exposure to cigarette smoke. In addition, an attempt was made to evaluate potential risk factors particular to American Samoa, such as exposure to traditional smoke ovens and to kapok, a natural silky fiber from trees indigenous to the area and thought by local medical personnel to be a potential allergen. Blood samples were obtained between December 2 and 17 from all patients and controls. Sera were tested by ELISA for the presence of RSV-specific IgM.

Maternal Antibody Studies

To examine the role of maternal antibody, previously drawn serum specimens from mothers of ten of the 13 patients from the case-control study who had a confirmed RSV infection by one of the tests described above, and 12 of the 14 well and IgM-negative controls, were obtained from banked serum at the Centers for Disease Control hepatitis control project on American Samoa (maternal sera for the remaining patients and well controls were not available). Ill controls and the one IgM-positive well control were excluded from this study to provide cleaner comparison groups. All maternal sera had been drawn between Jan 13 and Sept 25, 1986. Maternal sera were tested for detectable IgG to RSV by ELISA and for group-specific neutralizing antibody titer to RSV by a microneutralization assay.

RESULTS

The Outbreak

Review of hospital admissions for LRI in children less than 2 years old showed a seasonal pattern with increases during the last three months of each year, from 1984 to 1986 (Fig 1). During the last three months of 1986, more infants less than 6 months old were admitted with LRI than during any three-month period reviewed. The rates of hospitalization with LRI in American Samoa during the outbreak period were 60 of 1000 infants less than 6 months old compared with 22 of 1000 infants 6 to 11 months old, and 11 of 1000 children 12 to 23 months old.

Patients were admitted from all ten counties on the island. No significant difference was found in hospitalization rate by county.

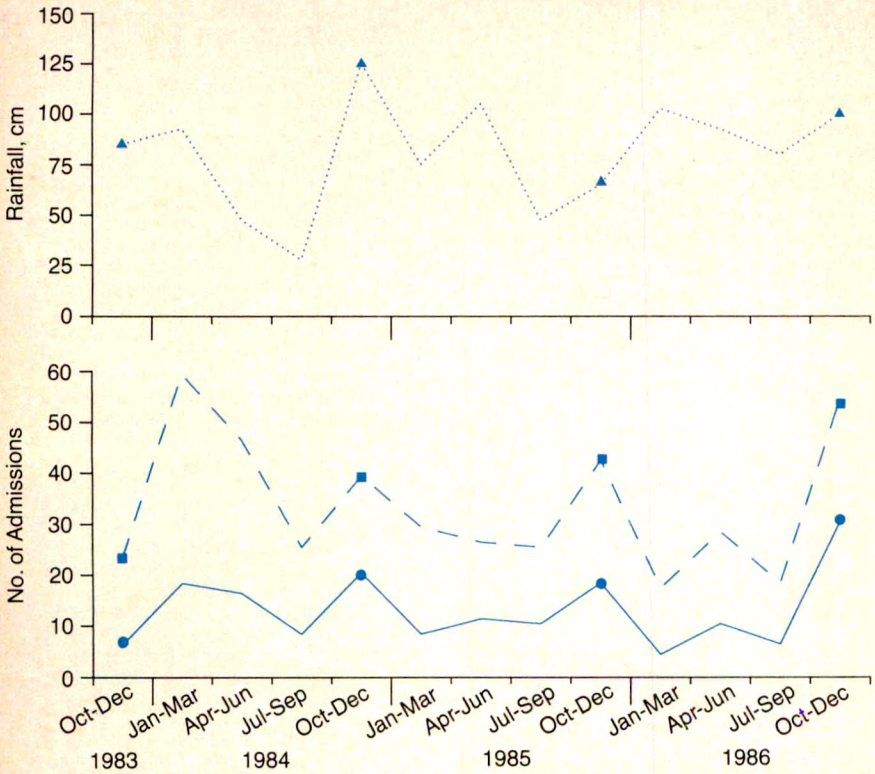
More children were also admitted to the ICU for LRI during the 1986 outbreak than during any three-month period in the previous three years. Ten of 54 hospital admissions for children less than 2 years old with LRI were to the ICU during the 1986 outbreak compared with three of 42, none of 39, and two of 23 during the same periods of 1985, 1984, and 1983, respectively (Table 2). (In 1986, four patients were admitted between December 17 and December 30, after our departure from the island, and three of the 47 children admitted before December 17 were hospitalized twice during the outbreak for a total of 54 admissions for comparison with the admission totals of previous years. None of the three repeated admissions were to the ICU.) During the 1986 season, seven children required intubation and two children died compared with one child requiring intubation and no deaths for the same period in 1985. When ICU admission rates among the hospitalized children with LRI were compared with rates of previous years, the rates had increased both for infants under 6 months old and for children between 6 months and 2 years old.

Some previous studies in tropical regions have shown an association between epidemics of respiratory illness and rainfall.[7,8] The total rainfall (obtained from the Economic Development and Planning Office, American Samoa) for each three-month period is shown with admissions for LRI (Fig 1). No significant correlation was found between rainfall and admissions for LRI by a Spearman correlation test, and

Table 1.—Summary of Study Groups

Field Investigation Carried Out Nov 17 to Dec 17, 1986

1. *Review of admission logs:* 54 admissions of patients <2 years old with lower respiratory tract illness from Oct 1 through Dec 30, 1986. (50 admissions were before Dec 17, including 3 readmissions, thus 47 individuals were admitted before Dec 17. Four admissions were after Dec 17.) Ten patients were admitted to the intensive care unit (ICU), all before Dec 17.
2. *Review of clinical data:* 45 of 47 charts were available for review. Clinical data were extracted from these 45 charts.
3. *Etiologic studies:* Specimens obtained from 34 of 47 patients, including 8 of 10 patients in the ICU.
4. *Case-control study:* 20 of 43 patients <1 year of age were available for inclusion in study, including 6 of 9 patients in the ICU. 60 controls were obtained.
5. *Maternal antibody study:* Maternal sera were available from 10 of 13 cases with evidence of respiratory syncytial virus infection and from 12 of 15 well controls from case-control study.



Hospital admissions for lower respiratory tract illness in children less than 6 months old (solid line) and less than 2 years old (broken line), and total seasonal rainfall in Samoa (dotted line).

Table 2.—Intensive Care Unit (ICU) Admission Rates for Lower Respiratory Tract Illness Among Children Less Than 2 Years of Age in American Samoa, October Through December, 1983-1986*

Year	No. of Admissions <6 mo	6-23 mo	Total
1983			
Hospitalized	6	17	**23**
ICU	2 (33)	0 (0)	**2** (9)
1984			
Hospitalized	20	19	**39**
ICU	0 (0)	0 (0)	**0** (0)
1985			
Hospitalized	18	24	**42**
ICU	2 (11)	1 (4)	**3** (7)
1986			
Hospitalized	30	24	**54**
ICU	7 (23)	3 (13)	**10** (19)

*Numbers in parentheses indicate percents of hospitalized patients in the ICU.

when plotted by month (data not shown), increases in admissions often preceded increases in rainfall within the same three-month period.

Etiologic Studies

Eighteen (53%) of the 34 patients tested had evidence of recent infection by RSV, either by positive nasal aspirate for RSV by ELISA or TR-FIA (nine of 18), detectable IgM to RSV (ten of 34), or fourfold titer rise in RSV-specific IgG in paired sera (three of 13). Five (63%) of the eight patients in the ICU had a positive test for RSV.

Adenovirus type 7 was cultured from one patient's nasal aspirate and echovirus type 13 was cultured from another. None of the other nine nasal aspirates yielded any viral growth.

The patient from whom adenovirus type 7 was isolated had no evidence of RSV infection. This same patient was the only one of 13 patients to show a fourfold titer rise to adenovirus type 7, and the only one of 18 patients tested to have adenovirus detected by TR-FIA on nasal aspirate. Two of the six patients tested for echovirus type 13 showed fourfold titer rises to this virus, including the one from whom echovirus was cultured. However, both of these patients also showed serologic evidence of RSV infection.

No fourfold titer rises to parainfluenza types 1, 2, and 3, influenza type A, or influenza type B occurred with sera from any of the 13 patients tested.

Clinical Characteristics

The combined clinical characteristics of patients with laboratory evidence of recent RSV infection compared with those in whom tests for RSV were negative and those whom we were unable to test are shown in Table 3. There were no significant differences between these groups in any clinical characteristic examined except that patients with positive tests for RSV were significantly younger than those in the other two groups ($P = .02$, Kruskal-Wallis). The difference in age may be partly explained by more vigorous testing of younger patients; excluding attempts at virus isolation, an average of 3.3 diagnostic tests per patient were administered to the 20 patients less than 6 months old compared with 2.8 tests per patient on the ten patients 6 to 12 months old and 2.3 tests per patient on the four patients 13 to 23 months old.

Of the two children who died, one was 20 months old with a maximum recorded temperature of 40°C, pleural and pericardial effusions, and right upper lobe infiltrate on roentgenogram. The other child, a 4-month-old infant had wheezing and hyperinflation visible with roentgenography, but had a temperature of 41°C, seizures with clear cerebrospinal fluid, and gastrointestinal bleeding. No specimens for etiologic studies were available from either of these two patients.

Case-Control Study

The results of the case-control study are shown in Table 4. The reported presence of a cigarette smoker in a child's household was found to be significantly associated with severe LRI in the infants studied. Eighteen (90%) of 20 hospitalized patients with LRI had a cigarette smoker in their household, compared with eight (53%) of 15 well controls (those with no history of respiratory illness) ($P = .02$, Fisher's exact test, two-tailed). This difference remains significant if the comparison is

limited to patients who tested positive for RSV (12 of 13 exposed) against the well controls ($P = .04$, Fisher's exact test, two-tailed). Thirty-four (76%) of 45 ill controls had a cigarette smoker in their households.

There were significantly fewer children sleeping in the households of ill controls than in the households of patients ($P = .005$, Wilcoxon rank sum test), but similar differences between patients and well controls were not significant. Ill controls were also older than patients, but when exposure to cigarette smokers was stratified by age group (newborn to 2 months, 3 to 5 months, and 6 to 11 months old) and by number of children sleeping in the household, the association with cigarette smoke described above remained significant.

No significant difference between patients who tested positive and patients who tested negative or between patients and controls was found in history of breast-feeding, history of underlying cardiorespiratory illness, birth weight, sex, gestational maturity, or exposure to smoke ovens or kapok. No significant difference between patients in the ICU and patients not in the ICU was found regarding any of the above risk factors (data not shown), but all of the six patients in the ICU in the study had a smoker in their household reported.

Six (30%) of the 20 patients were positive for RSV-specific IgM compared with five (11%) of the 45 ill controls and one (7%) of the well controls ($P = .01$, χ^2 test for trend).

Maternal Antibody Studies

All of the ten tested mothers of patients with evidence of recent RSV infection by at least one of the tests reported above had IgG to RSV in their serum (Table 5). Geometric mean titers of neutralizing antibodies to both group1 and group 2 strains of RSV were higher in the ten mothers of patients than in mothers of well controls, although not significantly so.

COMMENT

Our investigation documents an unusually severe outbreak of LRI among infants on American Samoa. The severity of the outbreak was manifested by not only an increase in hospitalizations but also intubations, ICU admissions, and deaths. During the three-year period reviewed, there was no change found in staff pediatricians or admission policies that would account for these increases. The outbreak was most evident among infants less than 6 months old. This age distribution, the clinical characteristics of most of the patients, and the laboratory results suggest that the outbreak was primarily caused by RSV. Many of the patients tested had recovered by the time of our investigation and we were thus unable to obtain acute sera and nasal aspirates from them that might have increased the proportion of positive results. The lack of significant differences in clinical characteristics (except in age, which is at least partly explained by the differences in numbers

Table 3.—Frequency and Distribution of Clinical Characteristics of Patients Less Than 2 Years of Age Hospitalized With Lower Respiratory Tract Illness in American Samoa, Oct 1 Through Dec 17, 1986*

Characteristic	Positive for RSV	Tested Negative	Not Tested
Wheezing†	15/18	14/16	9/11
Hyperinflation†	8/13	11/13	6/11
Infiltrates†	11/13	11/13	6/11
No. F†	8/18	7/16	4/11
Median temperature, °C (n) [range]	38.3 (18) [37.2-40.5]	38.3 (16) [37.2-40.5]	38.9 (10) [37.7-41.1]
Median WBC count, 10^9/L (n) [range]	1.14 (15) [.57-2.09]	1.43 (15) [.87-3.10]	1.46 (9) [.07-5.29]
Median respiratory rate, breaths/min (n) [range]	68 (18) [40-72]	66 (15) [25-92]	62 (10) [40-70]
Median age, mo (n) [range]	2.5 (18) [1-17]	9.5 (16) [1-19]	7.0 (11) [2-20]

*RSV indicates respiratory syncytial virus; WBC, white blood cell.
†Number of patients with characteristic/number of patients with information available on characteristic.

Table 4.—Frequency and Distribution of Potential Risk Factors in a Case-Control Study of Infants With Lower Respiratory Tract Illness in American Samoa*

	Cases		Controls	
Factor	Positive for RSV	Other	Ill	Well
Breast-fed in past	13/13	5/7	32/45	13/15
History of asthma	1/13	0/7	4/45	0/15
Family history of asthma	3/13	1/7	13/45	1/15
Previous cardiorespiratory illness	1/13	0/7	1/45	0/15
Cigarette smoker in household	12/13	6/7	34/45	8/15
Smoke oven used	11/13	7/7	33/45	13/15
Kapok trees nearby	6/13	2/7	24/45	5/15
Kapok pillow used	10/13	5/7	36/45	9/15
Born at term	11/13	7/7	43/45	14/15
No. F	6/13	3/7	27/45	6/15
Median birthweight (range), kg	3.7 (2.6-4.4)	3.6 (3.2-4.5)	3.5 (2.4-4.8)	3.5 (2.4-4.6)
Median No. of children sleeping in house (range)	4.0 (2-11)	5.0 (2-7)	3.0 (1-18)	3.0 (1-9)
Smoke oven use/week (range)	1.0 (0-2)	1.0 (1-3)	1.0 (0-7)	1.0 (0-7)
Median age (range), mo	2.0 (0-2)	1.0 (0-9)	6.0 (1-10)	2.0 (0-8)
Positive serum IgM	16/13	0/7	5/45	1/15

*RSV indicates respiratory syncytial virus. Data are number of patients with factor/total number of patients.

Table 5.—Maternal Antibody Study in American Samoa, 1986*

Factors	Mothers of Cases Positive for RSV	Mothers of Well Controls
No. (%) with detectable IgG/total No. tested	10/10 (100)	10/12 (83)
Neutralizing antibody (GMT)		
Group 1	1:26†	1:11†
Group 2	1:29‡	1:16‡

*RSV indicates respiratory syncytial virus; GMT, geometric mean titers of highest possible dilutions (serum unavailable on one case and one control). For mothers of cases positive for RSV, No. of patients with GMT is 9; for mothers of well controls with GMT, 11.

†$P = .12$.

‡$P = .21$.

of tests performed per age group) between patients who were positive, negative, and untested for RSV supports the possibility that at least some of the patients who tested negative for RSV and patients who were untested for RSV might have had positive results with more vigorous testing. The failure to isolate RSV is not surprising considering the long shipping distance for specimens and the lability of the virus.

Based on the 1980 population census figure of 983 infants (less than 1 year of age) in American Samoa, the proportion of infants who were hospitalized with LRI during the outbreak can be estimated to have been no less than one of 24 infants. This rate is higher than most rates reported from studies in the United States and England where rates of hospitalization for RSV in infants have varied between one of 40 and one of 200, depending on the methods of study, locality, and socioeconomic status of the infants studied.[4,5,9]

As an explanation for the increased severity of the outbreak in 1986 compared with those in previous years, we considered the possible role of year-to-year antigenic differences in the strain(s) of RSV. Two major groups of RSV strains have been identified by differences in reaction patterns against panels of monoclonal antibodies.[10,11] Although it remains unclear whether the two groups have different clinical effects,[11,12] it is possible that the antibodies, or lack thereof, induced in mothers by the strains of previous years and passively transferred to infants born in 1986 left these infants particularly susceptible to severe disease from RSV infection in 1986. Unfortunately, we did not have isolates from this and previous years to investigate this possibility. We did look for differences between mothers of patients and controls in neutralizing antibodies against representative viruses of the two groups of RSV strains. These studies showed no significant difference between mothers of patients and mothers of controls, but the strains we tested may not have been good enough proxy for the outbreak strain(s) or we may not have used a test that would identify critical differences.

Several previous studies have suggested that neutralizing antibodies in cord blood appears to protect against infection and/or moderate the severity of disease.[13-15] Studies of isolates and cord blood from affected and unaffected children and studies to explore any correlation between yearly variations in predominating groups of RSV and hospitalization rates are needed to determine if strain differences are important in the variation in severity of RSV outbreaks.

Concurrent increases in environmental irritants or allergens might also influence the severity of illness in RSV outbreaks. Our study did not show any obvious allergic risk factors in this outbreak.

A significantly greater number of infants hospitalized during this outbreak with LRI than controls without respiratory tract illness had cigarette smokers in their households. Increased risk of LRI in infants exposed to parental smoking has been previously described.[16-21] Sims et al,[18] Pullan et al,[19] and Pullan and Hey [20] found significantly increased exposure to parental smoking among infants hospitalized with RSV infection compared with school, birth register, and physician-referred controls. Fergusson et al[21] followed up a cohort of 1180 infants for one year and found that infants exposed to maternal smoking had a higher risk of LRI, but a lower risk of upper respiratory tract illness, and suggested that maternal smoking facilitated spread of infection to the lower respiratory tract.

In our study the increased proportion of infants exposed to cigarette smokers in the home is paralleled by an increase in proportion of infants with serologic evidence of RSV infection as measured by serum IgM. This suggests that the risk of severe LRI caused by RSV is increased by passive smoking. It is not clear whether this effect of passive smoking is due to an increased risk of infection or due to an increase in severity once infection has been acquired. The proportion of infants exposed to cigarette smokers increased with hospitalization and admission to the ICU when analysis was limited to only ill infants, but this trend was not significant. Due to time limits and study conditions, questionnaire responses in the case-control study were not confirmed by home visits or medical record review, nor was any effort made to quantify cigarette exposure. Nevertheless, our findings reinforce the importance of limiting infants' exposure to cigarette smoke to reduce the risk of severe LRI. Further studies would be useful to assess the effect of passive smoking on laboratory-documented infection and to better evaluate any possible effect on severity of illness once acquired.

In summary, LRI in children less than 2 years old appears to have a seasonal pattern in American Samoa. The outbreak of LRI in 1986 was more severe and affected younger infants than did outbreaks of the previous two years. The majority of children hospitalized with LRI had evidence of RSV infection. The mere presence of antibody to RSV in mothers' sera did not protect their infants from illness. Passive smoking was significantly more prevalent among infants with severe RSV-associated LRI than among well controls.

We gratefully acknowledge the help of Barbara Coven, MD and Elizabeth Barnett, MD, who assisted in the clinical studies, as well as Cecilia Tsou, MS, John Hierholzer, PhD, Paul Pinsky, MPH, David Morens, MD, Jill McCreedy, MT, and the personnel of the Centers for Disease Control Hepa-

titis Control Project on American Samoa, the Department of Public Health of American Samoa, and the government of American Samoa. In addition, Abbott Laboratories, South Pasadena, Calif, kindly provided materials for RSV ELISA testing on nasal aspirates in the field, and Vaughn Trader assisted in preparation of the manuscript.

References

1. Leowski J: Mortality from acute respiratory infections in children under 5 years of age: Global estimates. *World Health Stat Q* 1986;39:138-144.

2. Berman S, McIntosh K: Selective primary health care: Strategies for control of disease in the developing world: XXI. Acute respiratory infection. *Rev Infect Dis* 1985;7:674-688.

3. Denny FW, Clyde WA Jr: Acute lower respiratory tract infections in nonhospitalized children. *J Pediatr* 1986;108:635-645.

4. Hall CB: Respiratory syncytial virus, in Feigin RD, Cherry JD (eds): *Textbook of Pediatric Infectious Disease*. Philadelphia, WB Saunders Co, 1981, pp 1247-1267.

5. McIntosh K, Chanock RM: Respiratory syncytial virus, in Fields BN, Knipe DM, Chanock RM, et al (eds): *Virology*. New York, Raven Press, 1985, pp 1285-1304.

6. Henderson FW, Clyde WA Jr, Collier AM, et al: The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J Pediatr* 1979;95:183-190.

7. Spence L, Barratt N: Respiratory syncytial virus associated with acute respiratory infections in Trinidadian patients. *Am J Epidemiol* 1968;88:257-266.

8. Monto AS, Johnson KM: A community study of respiratory infections in the tropics: I. Description of the community and observations on the activity of certain respiratory agents. *Am J Epidemiol* 1967;84:78-91.

9. Belshe RB, Van Voris LP, Mufson MA: Impact of viral respiratory diseases on infants and young children in a rural and urban area of southern West Virginia. *Am J Epidemiol* 1983;117:467-474.

10. Anderson LJ, Hierholzer JC, Tsou C, et al: Antigenic characterization of respiratory syncytial virus strains with monoclonal antibodies. *J Infect Dis* 1985;151:626-633.

11. Mufson MA, Belshe RB, Orvell C, et al: Respiratory syncytial virus epidemics: Variable dominance of subgroups A and B strains among children, 1981-1986. *J Infect Dis* 1988;157:143-148.

12. Hendry RM, Talis AT, Godfrey E, et al: Concurrent circulation of antigenically distinct strains of respiratory syncytial virus during community outbreaks. *J Infect Dis* 1986;153:291-297.

13. Glezen WP, Taber LH, Frank AL, et al: Risk of primary infection and reinfection with respiratory syncytial virus. *AJDC*. 1986;140:543-546.

14. Glezen WP: Incidence of respiratory syncytial and parainfluenza type 3 viruses in an urban setting. *Pediatr Virology* 1987;2:1-7.

15. Glezen WP, Paredes A, Allison JE, et al: Risk of respiratory syncytial virus infection for infants from low-income families in relationship to age, sex, ethnic group, and maternal antibody level. *J Pediatr* 1981;98:708-715.

16. Colley JRT, Holland WW, Corkhill RT: Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. *Lancet* 1974;2:1031-1034.

17. Harlap S, Davies AM: Infant admissions to hospital and maternal smoking. *Lancet* 1974;1:529-532.

18. Sims DG, Downham MAPS, Gardner PS, et al: Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. *Br Med J* 1978;1:11-14.

19. Pullan CR, Toms GL, Martin AJ, et al: Breast-feeding and respiratory syncytial virus infection. *Br Med J* 1980;281:1034-1036.

20. Pullan CR, Hey EN: Wheezing, asthma, and pulmonary dysfunction ten years after infection with respiratory syncytial virus in infancy. *Br Med J* 1982;284:1665-1669.

21. Fergusson DM, Horwood LJ, Shannon FT: Parental smoking and respiratory illness in infancy. *Arch Dis Child* 1980;55:358-361.

Book Review

Ambulatory Pediatric Care, edited by Robert Dershewitz, 944 pp, $49.50, Philadelphia, JB Lippincott, 1988.

As the editor states in the preface to *Ambulatory Pediatric Care*, most children seen in office practice are "fundamentally well." Consequently, this text emphasizes issues of office practice and general health maintenance.

The first six sections contain pearls for both practitioners and residents in pediatric and family practice. Topics covered include the content of well-child visits, nutrition, accident prevention, school health, and developmental and behavioral pediatrics. The behavioral section is a particularly well-written overview of important issues that may have a profound impact on the psychosocial health of the family: divorce, single parenting, career and motherhood, death of a family member, sleep disturbances, and chronic illness. The chapters titled "The Constant Complainer" and "Dealing With Difficult Parents" should be read by all residents.

The developmental pediatric section, however, could be strengthened by more practical information. It would help to have a description of the available language and developmental screening tests (including their strengths and weaknesses) as well as an explanation of personnel needed to administer these tests within the confines of a private practice. More space should be devoted to the developmental section in subsequent editions.

The child abuse section also deserves expansion. More detail and guidance could be provided in a discussion of the definition of child abuse and neglect, the various techniques used to interview victims and their parents, the importance of documenting injuries, the thought process involved in formulating impressions, and the physician's role in the legal process. The addition of illustrations, diagrams, and a few more references would also strengthen the section.

The remaining 650 pages of the text are devoted to common signs, symptoms, and illnesses encountered in outpatient practice. Clinical problems are described in terms of variations in presentation, differential diagnosis, workup, treatment and management, and indications for referral or hospitalization. Each of these sections may be scanned in a few minutes and will serve to refresh the memory or point the physician in the right direction until there is time to consult more-detailed sources. A helpful annotated bibliography follows each section.

This readable text will assist the busy practitioner and the student of pediatrics. It has a place in the library of those providing primary health care services for children.

GERALD B. HICKSON, MD
Vanderbilt University
Nashville, TN 37232-5577

onnaught
TP Special
ervice

Dependable Delivery Service

Just dial toll-free
1-800-VACCINE
(1-800-822-2463)
from 8AM to 8PM

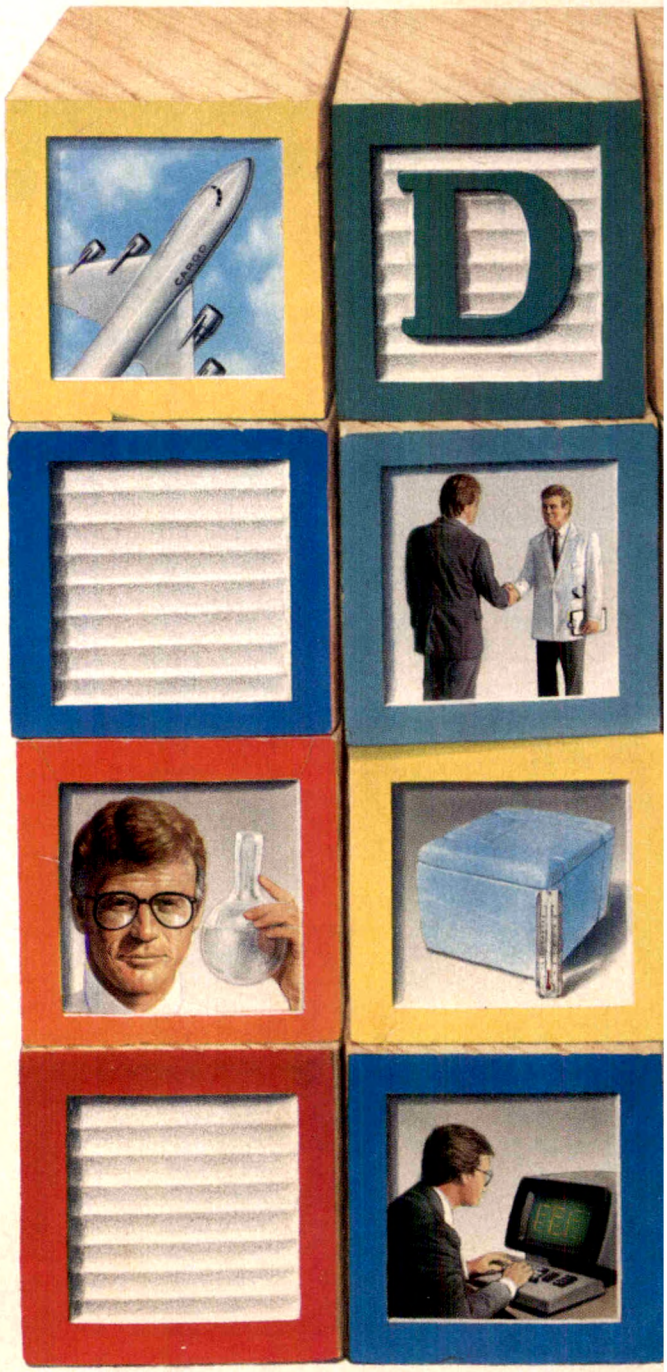
Temperature-controlled Shipping

Product integrity ensured
on a year-round basis
through special temperature
indicator and insulated
packaging

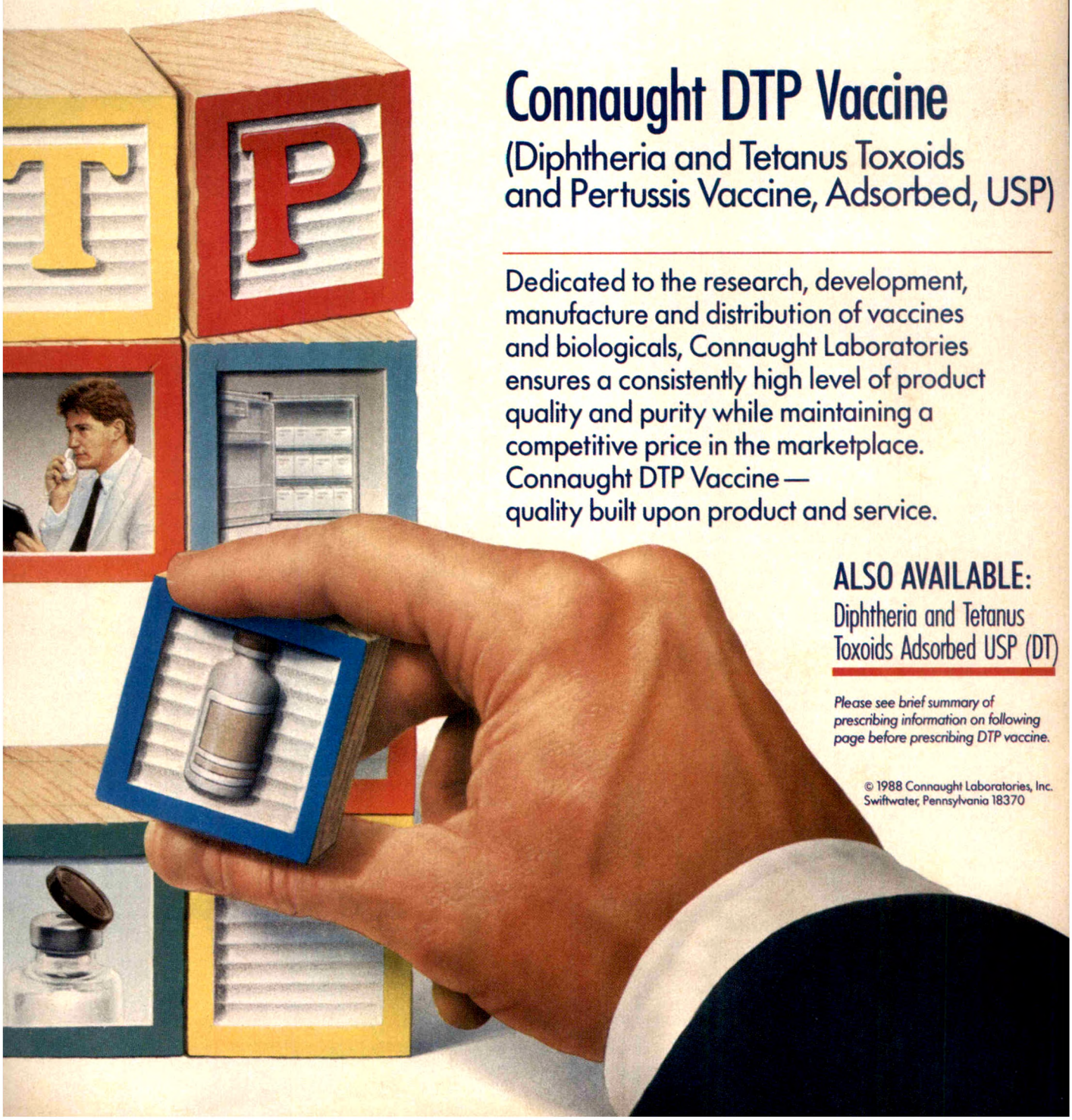
Physician Support Materials

Vaccine Monitoring Kit
to simplify compliance
with the National
Childhood Vaccine Injury Act

® CONNAUGHT
LABORATORIES, INC.
pecialist in vaccines and biologicals



BUILDING BLOCKS FOR CHILDREN'S HEALTH



Connaught DTP Vaccine

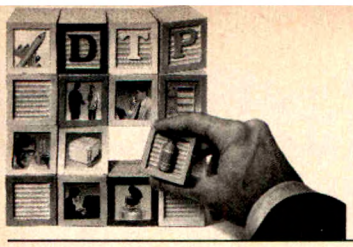
(Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, USP)

Dedicated to the research, development, manufacture and distribution of vaccines and biologicals, Connaught Laboratories ensures a consistently high level of product quality and purity while maintaining a competitive price in the marketplace. Connaught DTP Vaccine — quality built upon product and service.

ALSO AVAILABLE:
Diphtheria and Tetanus Toxoids Adsorbed USP (DT)

Please see brief summary of prescribing information on following page before prescribing DTP vaccine.

© 1988 Connaught Laboratories, Inc.
Swiftwater, Pennsylvania 18370



Connaught DTP Vaccine

(Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, USP)

BRIEF SUMMARY

Before prescribing, please consult the complete package circular.

INDICATIONS AND USAGE: For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping chough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS: *Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.*

Absolute contraindications.

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or local neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered an absolute contraindication to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.

WARNINGS: *This vaccine must NOT be used for immunizing persons 7 years of age and older.*

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS AN ABSOLUTE CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurological disorders, must be decided on an individual basis. Please refer to ACIP recommendations for the following categories of patients:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.**
2. **Infants and children with neurologic events temporally associated with DTP.**
3. **Incompletely immunized children with neurologic events occurring between doses.**
4. **Infants and children with stable neurologic conditions.**
5. **Children with resolved or corrected neurologic disorders.**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month, otherwise, the patient should be vaccinated while still on therapy.

Persons receiving immunosuppressive therapy, a recent injection of immune globulin, or having an immunodeficiency disorder, may not generate an adequate immunologic response to the DTP vaccine.

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Please refer to ACIP recommendations.

PRECAUTIONS

GENERAL

Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. However, these observations were not noted by Barkin, R.M., et al. Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics). Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.

TABLE 1. Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever >38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

*Number of adverse events per total number of doses regardless of dose number in DTP series.
†Occurring within 7 days of DTP immunization.

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent. If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS. It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2–6 months old and that approximately 85% of SIDS cases occur at ages 1–6 months, with the peak incidence occurring at 6 weeks–4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3–9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged.

The following illnesses have been reported as temporally associated with the vaccine; neurological complications including cochlear lesion, brachial plexus neuropathies, paralysis of the radial nerve, paralysis of the recurrent nerve, accommodation paresis, and EEG disturbances with encephalopathy. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.

Product information as of July, 1986

® CONNAUGHT® is a trademark owned by Connaught Laboratories, Inc.

Mfd. by: CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.
MKT0246 12/88
Printed in U.S.A. 0585

International Adoption

An Introduction for Physicians

Margaret Hostetter, MD, Dana E. Johnson, MD, PhD

Despite great progress in the medical treatment of infertility, approximately 1 million American couples are unable to bear children.[1] The high rate of involuntary infertility, coupled with a decrease in the number of US-born infants available for adoption,[2] has prompted a tremendous growth in the number of international adoptions. In the past 10 years the number of children adopted from abroad has almost doubled[3] and the number of American agencies handling international adoptions has almost tripled.[4] This trend has reached the point where it is rare for a primary care physician not to be following up at least one international adoptee. However, the number of children is yet insufficient for most physicians to have had extensive exposure to either the process of international adoption or the variety of medical problems that may afflict these children.

The purpose of this article is to provide an orientation to this field. Much of the information presented is based on our experience and anecdotes from adoption professionals and adoptive families. One reason why this is the case is that little information on these children is available in the scientific literature. Equally important, however, is the need to communicate the personal and emotional aspects of international adoption. These are observations that do not readily lend themselves to quantitation but, for reasons discussed below, are among the most important aspects for physicians to understand. From our experience it is clear that parents need assistance from their physician during the process of adopting a child from another country. We hope to provide the information needed to help health care professionals assist parents in making well-reasoned decisions and support them throughout their lifelong commitment to parent a child from abroad.

Accepted for publication December 2, 1988.

From the International Adoption Clinic, Department of Pediatrics, University of Minnesota Medical School, Minneapolis.

Reprint requests to Box 211, University of Minnesota, Harvard Street at East River Road, Minneapolis, MN 55455 (Dr Johnson).

INTERNATIONAL ADOPTION DEMOGRAPHICS

In 1987, 10 097 orphans from 79 countries entered the United States.[3] This represented a 189% increase over 1978, when 5315 children from 81 countries were admitted. From the number of countries involved, acquiring background information on the diverse origins of these children may appear overwhelming; however, virtually the same 14 Asian and Latin American countries have accounted for over 87% of international adoptions throughout this 10-year span (Table 1). Of these countries, Korea is the single most important source of orphans, accounting for more than half of the children during both years. Despite war, famine, political turmoil, etc, there has not been a marked change in the percentage of children coming from various areas of the world (Table 1). One reason so few countries account for the major sources of orphans is that some nations forbid outright the emigration of orphans. Few, if any, children come into the United States from the African continent, from countries that are predominantly Moslem, or from nations whose governments are in conflict with the policies of the United States.

Parents who adopt internationally are generally college-educated, white, suburban couples earning approximately $36 000 per year.[4] Both parents are usually in their mid-30s, have been married for 7 years, and have no other children. Though two-parent adoptions are most common, single-parent adoption is becoming more frequent, particularly with Indian and Latin American children. As with two-parent families, single parents are generally professional women in their 30s with sufficient income to pay both the adoption costs and child care expenses. Not surprisingly, infants (<1 year, 64% [1986])[3] and toddlers (1 to 4 years, 21%) comprise the majority of adopted children. A fact which is not as easily reconciled is the predominance of female adoptees (1.3:1, female-male ratio [1986]), particularly when many foreign agencies prohibit the specification of sex for the first child in the family. This phenomenon may be the result of a number of factors, including a lower infant mortality rate for females, a lower status for female children in some countries, an increase in the rate of adoption by single female parents, and what seems to be a slight preference for female children among two-parent families considering international adoption.

Table 1.—Origins of International Adoptees, %

Continent	1978 (N=5315)	1987 (N=10097)
Europe	2.7	1.2
Asia	70.7	75.4
Korea	57.3	58.5
India	2.8	8.0
Philippines	5.4	5.9
Taiwan	0.9	0.7
Africa	0.3	0.2
Oceania	0.3	<0.1
North America	11.9	9.6
Mexico	2.9	1.8
Guatemala	1.0	2.9
Honduras	0.5	1.1
El Salvador	1.8	1.3
Costa Rica	1.6	0.7
South America	14.1	13.5
Brazil	0.3	1.8
Chile	0.7	2.4
Columbia	11.3	7.2
Paraguay	...	1.8
Peru	0.7	0.8
Total countries	81	79

Table 2.—Process of International Adoption

US Agency	Immigration and Naturalization Service	Foreign Agency
	Preadoption Process	
Informational meeting	...	...
Formal application	...	...
Home study	...	...
	Filing form I-600A "Application for Advance Processing of Orphan Petition"	Formal application
	...	Child referral
	Filing form I-600 "Petition to Classify Orphan as an Immediate Relative"	...
	Visa investigation	
	Visa issued	
	...	Legal adoption in host country*
	Arrival of the Child	
Progress reports to foreign agency	...	...
Assistance with US adoption procedures	...	...
...	Naturalization	...

*Only for certain countries.

THE PROCESS OF ADOPTING FROM ABROAD

Though state regulations covering adoption of US-born children vary substantially, federal regulations, administered through the Immigration and Naturalization Service (INS), have effectively standardized the major steps in the process of international adoption throughout the United States (Table 2). Standardization, however, should not be equated with simplification as the parents must deal with several separate agencies—often simultaneously—throughout the year(s)-long process. The mountain of paperwork, indeterminate and often lengthy waiting periods, and dependence on domestic and foreign bureaucracies lead to frustration, anxiety, and a general feeling of impotence in adoptive parents during this time. Physicians must therefore be aware of the mechanics of adoption to provide empathetic support during the months and often years that the family may be waiting for their child.

Formal entry into the process of international adoption is through a state-licensed adoption agency or independent adoption facilitator. One of the principal functions of the agency or facilitator is to determine the ability of the prospective adoptive parents to care for an adopted child. The document or "home study" generated through this investigative process requires multiple in-the-home and out-of-the-home interviews with the prospective adoptive parents and other family members and can take 6 or more months to complete. A sample of the issues that must be addressed in the home study are listed in Table 3. A favorable recommendation from the home study is required before any action is taken by any other agency. While some adoption agencies provide little more than the home study, most offer an array of services, including parent support groups, preadoption and postadoption counseling, child care classes, and assistance in locating an adoptable child and fulfilling the requirements stipulated by the foreign agency and country. The spectrum of the services offered is generally reflected in the agency's fees.

Before or during the home study, the parents choose a foreign agency or program to which they will apply for their child. American agencies often have specific recommendations based on their experiences, but parents are often free to identify other sources of referral. As one could imagine, many ways exist for foreign agencies to procure a child for adoption. Therefore, prospective adoptive parents should be counseled to deal only with reputable foreign agencies whose operational guidelines are known to be ethically sound.

Table 3.—Topics That Must Be Addressed in the Home Study

- Motivation for adoption
- Capacities and attitudes
- Personal relationships and personality
  - marriage
- Health, age, nationality, and race
- Employment and finances
- Religious, moral, and ethical beliefs and practices
- Education
- Environment
- Child-rearing practices
- Family interactions
- Cultural issues

The application requirements stipulated by the foreign agency are determined by considering the adoption regulations of the host country, the background and mission of the agency itself, and the agency's desire to place the child in what they believe is an optimal home environment. The resulting

restrictions on marital status, length of marriage, previous divorce, income, family size, parent age, religious affiliation, fertility status, and health (eg, weight standards may be applied) may severely limit the options of potential parents. Consequently, for those individuals who are single, approaching 40 years of age, obese, etc, the choice of age, health status (special needs), or nationality for their child may be severely restricted.

As soon as the home study is complete, initial application to the INS can be made. This application can and probably should be made well in advance of identification (referral) of a specific child by the foreign agency. In brief, this initial process, termed "Filing of the Application for Advance Processing of Orphan Petition" (I-600A), allows the federal government to determine if the parents are qualified to bring an orphan into the United States (citizenship), are free of a criminal record (Federal Bureau of Investigation review of fingerprints), and are able to care for the child after arrival (agency home study).

Assuming that the parents' application to the foreign agency is accepted, the next step is waiting for the referral of a specific child. The referral packet sent to the parents generally contains some information on the background of the child, his or her present condition, and one or more pictures. The medical information that the parents receive at this time varies in quantity and quality. Some foreign agencies provide an extensive dossier on the biologic parents, circumstances surrounding labor and delivery, a medical history of the child, sequential growth parameters, and the results of a recent physical examination and developmental assessment. Others provide only cryptic comments stating that the child is "healthy," "moderately malnourished," or "slightly developmentally delayed." A desire to have this medical information interpreted often brings the parents to their physician.

Most physicians, justifiably, feel uneasy about evaluating a child living thousands of miles away solely based on the sparse information contained in the medical record. However, most parents are realistic and usually desire only information rather than solid assurances of health or future developmental normality. Infants are reasonably easy to assess. Development does not significantly differ among racial groups during the first months of life. The major exception to this general rule is the delay in the acquisition of gross motor developmental milestones seen in cultures, such as Korea, where the child is held most of the time rather than being allowed to explore on his or her own. Growth, while differing significantly between national groups and even among different ethnic groups within the same country (eg, Indian vs Spanish ancestry in Latin America), usually parallels standard American growth curves. This is especially true for Korean children whose height, weight, and head circumference are usually within American norms during infancy. Because many international adoptees are premature infants, growth and development must be evaluated based on corrected gestational age rather than actual age. Because the mother's obstetric history may be unreliable or unknown, a 1-month lag in growth and development in an infant thought to be full-term is more often incorrect gestational dating than true developmental delay. Common problems that occur in infancy such as diarrheal disease can complicate the interpretation of the available data. In this situation, growth (due to malnutrition) and development (due to illness and prolonged hospitalization) can be temporarily, though not necessarily permanently, affected. When questionable situations arise, an additional month or two of observation will often clarify the situation. In our experience, both the American and foreign agencies are often willing to delay the final decision on a referral until patterns of growth and development are reliably established or until confirmatory diagnostic tests or evaluations are obtained.

Older children present more of a challenge. First, the child's actual age may not be known. Because malnutrition and physical and emotional neglect may have affected linear growth, motor and intellectual development, and bone age, the only physical parameters somewhat useful in determining the child's age may be tooth eruption, the stage of pubertal development, and possibly head circumference. Second, significant gaps in the child's history usually exist. Because older international adoptees may have been abandoned and forced to live in the streets, one can only imagine the illnesses, deprivation, and abuse they may have suffered. Often the only information that can be given to parents is the proportionality of the child's growth parameters, a guess as to the child's actual age, concerns as to the effects of long-term malnutrition (if present) on future intellectual development, and the possibility that emotional or physical neglect and abuse (if suggested by the history) may place their child at risk for temporary or permanent behavioral disorders.

Although medical expertise is needed, effective counseling of adoptive families also requires insight into the parents' outlook at this point in the adoption process. While it appears that adoptive parents have an opportunity that is not afforded to biologic parents—to accept or refuse a specific child—in reality, adoptive parents often feel they have little freedom of choice. The time spent waiting for the referral of a child is often lengthy and the waiting only intensifies the parents' longing for a child. In addition, they may believe that refusal of a specific child may jeopardize their chances for referral of another child. Consequently, when a file on a specific child is received, their joy and desire to have that child as part of their family often overwhelms their ability to be objective about existing problems. This is a time when prospective parents must be as honest as possible with themselves and with each other. Physicians should facilitate this candid dialogue and provide the impartial medical analysis that the parents are professionally and emotionally incapable of undertaking. As in any counseling situation, physicians should avoid interjecting their personal biases. The goal should be to ensure that the parents are accepting a child they honestly feel capable of parenting rather than accepting any child to avoid further waiting.

The second important fact to remember is the extraordinary importance of the child's picture to the parents. This image of a child enclosed with the referral documents becomes an image of *their* child—not of a child they will have, but a child that they *now* have. When the envelope is opened, they become parents

to that child almost as certainly as if they were holding a slippery, screaming infant in the delivery room. To paraphrase St John, in the photograph, indeed, "the word becomes flesh."

To those who have not experienced this phenomenon, this description may seem hyperbolic. It is not. Parents who have seen the child's picture, even faced with severe unexpected medical complications, can have an extraordinarily difficult time rejecting the referral. In situations where the child dies in the foreign country or the adoption is incomplete for another reason, parents undergo a grieving process similar to that for a biologic child. Therefore, in situations where serious medical issues have been raised, an offhand suggestion to "just pick another one" is not merely inappropriate, it is as offensive as suggesting that parents give up their biologic child. This type of remark, which is made far too often by medical personnel, indicates to the adoptive parents that their health care provider is ignorant of the process of international adoption, is not empathetic to their plight, and is incapable of being an advocate for their child. That physician is unlikely to see that family again.

In counseling individuals or couples who are anguishing over the decision of whether to accept a child with significant medical problems, it is helpful to frame the discussion in the context of what is best for the child rather than what, one might paternalistically believe, is best for the parents. If, after examining their capabilities, the parents feel incapable of caring for the child, the physician can gently suggest that the child might be better off with another family who may have the needed resources. Adoptive parents must be made to feel that they are protecting rather than abandoning their child.

After accepting a referral, the next step in the process is to file form I-600 "Petition to Classify Orphan, as an Immediate Relative" with the INS. With this petition, the parents must provide proof of the orphan's age and acceptable documentation that the child is legally available for adoption. Evidence must also be provided that adoption requirements, if any, of the state of the orphan's proposed residence have been met.

Assuming that all requirements are met and the petition is approved, the INS cables the orphan petition to the American consulate or embassy closest to the child. A consular officer then conducts an overseas orphan investigation to ensure that the child is indeed an orphan as defined in immigration law, and arranges for the child to be examined by a physician to ensure that the child does not have a significant illness or disability which is not described in the orphan petition.

The quality of this visa medical evaluation is so extraordinarily variable that an assurance of health should be viewed by parents and their physician as confirming only that the child is alive rather than free of unsuspected medical problems. Parents may ask their physician to interpret the classification system (A, B, or C) used by the federal government in the examination. Class A includes psychiatric disorders, mental retardation, and dangerous contagious diseases, including chancroid, gonorrhea, granuloma inguinale, infectious leprosy, lymphogranuloma venereum, infectious syphilis, active tuberculosis, and, as of December 1, 1987, human immunodeficiency virus (HIV) infection.[5] Parenthetically, testing for HIV-seropositivity is *not* required in children younger than 15 years unless they have a history (hemophilia or HIV-positive parent) or signs and symptoms suggestive of the disease.[5] Therefore, few children will actually be screened for acquired immunodeficiency syndrome (AIDS) before their arrival in the United States. Class B is defined as "physical defect, disease, or disability serious in degree or permanent in nature amounting to a substantial departure from normal physical well-being." Although this category sounds ominous, minor cosmetic defects, such as occipital hemangiomas (stork bites), are often placed in class B. Class C is defined as "minor conditions." If the overseas investigation is successfully concluded, the child is issued a permanent resident's visa and can now be admitted to the United States.

At this point some countries, agencies, or both, particularly in Central America and South America, require one or both parents to travel to the country before the child's departure. Because the parents must remain in the country for 7 to 14 days, this trip entails substantial out-of-pocket expenses and a considerable amount of time lost from work. In the majority of international adoptions, however, no travel is required of the parents.

By now the parents have invested not only considerable time but a substantial amount of money. Fees charged by agencies in the United States vary, but are usually between $1500 and $3000. Foreign agency fees vary even more, from a low of approximately $1000 upward to $7000 through $10 000. Even if the parents are not required to travel to the country of origin, some type of travel fee, usually $1000 to $2000, is required for transportation of the child to the United States. Adding notary, document, and INS fees, the cost of emigrating a child into the United States usually ranges from $5000 to $10 000, but can be higher depending on the program.

Waiting for the child once the paperwork has been completed can seem an eternity for expectant adoptive parents. While the wait can be mercifully short compared with other parts of the adoption process, unforeseen events can delay the child's journey. When the child finally does arrive, those present witness a true catharsis. The months and years spent waiting, the costs, and the overwhelming amount of paperwork that has been filed are now justified as the nervous parents wait at the end of the boarding ramp for the escort to disembark with their child. Because several children usually arrive at once, imagine 20 to 30 close friends and relatives, numerous video and still cameras, dozens of balloons and presents for *each* child mixed with the normal confusion of a busy airlines terminal. This event is a fitting climax to the process, one that should be witnessed at least once by every physician caring for adopted children from abroad.

To complete the process, adoption proceedings in the United States can begin after a defined 3- to 6-month waiting period, depending on the state of residence. Formal adoption in the United States is recommended, even for children who have been legally adopted abroad, because it provides the child a US birth certificate. Once the child is formally adopted, parents can apply for citizenship for their child. During this

time the US agency is involved with filing postplacement reports for the foreign agency and may offer postadoption services. While the naturalization ceremony or even the trip to the airport may seem to be the fulfillment of the process of international adoption, parents and physicians alike must remember that these points are not an ending but the beginning of a lifelong commitment to parent a child from another culture.

For those interested in an in-depth discussion of the regulations and procedures governing international adoption, the INS publishes a booklet entitled "The Immigration of Adopted and Prospective Adoptive Children." This publication (Form M-249) is for sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

THE PHYSICIAN'S ROLE AFTER THE CHILD'S ARRIVAL

The physician's three principal goals, after the child arrives, should be to ensure that: (1) the child is free of diseases that may have an adverse affect on the health of the child or the adoptive family, (2) medical conditions previously known to be present are appropriately evaluated and cared for, and (3) parents recognize that they have made a lifelong commitment to parent a child from a culture different from theirs. The child's first visit to the physician should be within 2 weeks of his or her arrival in the United States. From our experience, it is highly unusual for children to arrive with severe medical problems that demand immediate attention; however, in a retrospective survey of 128 international adoptees, 49% of the children had an acute infection (otitis media, upper respiratory tract infection, or varicella, to name a few) within 1 month of their arrival.[6] Therefore, unless a febrile illness intervenes, parents should be discouraged from bringing the child to their physician before the adverse affects of the long journey have resolved.

Our experience in the International Adoption Clinic at the University of Minnesota, Minneapolis, has emphasized that the prospective application of well-chosen screening tests will reap great benefits in preventive health care for these children. For example, in our prospective study of 52 consecutive international adoptees, the combination of history, physical examination, and screening tests elucidated an unsuspected medical diagnosis in 63% of these children, even if the child had been seen on one or more occasions by a US physician.[7] The screening tests of greatest utility are featured in Table 4.

Table 4.—Screening Tests Used for International Adoptees

Hepatitis B profile, to include hepatitis B surface antigen and antibodies to hepatitis B surface and core antigens*
Purified protein derivative (Mantoux) test with *Candida* control
Fecal examination for ova and parasites†
VDRL
Complete blood cell count with erythrocyte indexes
Urinalysis and urine culture for cytomegalovirus
Vision and hearing screening

*All patients who are positive for hepatitis B surface antigen are evaluated for the presence of hepatitis B e antigen and transaminase elevation.

†Symptomatic children, especially those from India, also receive stool cultures for *Salmonella, Shigella, Yersinia,* and *Campylobacter.*

Infectious Diseases

More than half of the medical diagnoses made in our clinic were infectious diseases, and these commonly reflected the prevalence of tuberculosis, hepatitis B, or cytomegalovirus (CMV) in the countries of origin. Thus, while these infections are not peculiar to adopted children, they are an expression of the environment from which these children come. Again, our experience with these children has indicated that these screening tests should not be selectively applied according to age, country of origin, or asymptomatic vs symptomatic presentation. All international adoptees, regardless of age or country of origin, must have a thorough health examination, with directed screening tests, shortly after arrival in the United States. Although the screening tests in Table 4 are self-explanatory and should be readily available to any physician, some discussion is in order.

Hepatitis B

The hepatitis B profile, rather than simple testing for hepatitis B surface antigen, is recommended. In our experience, approximately 60% of our children with acute or chronic hepatitis B would have been misdiagnosed had only the latter screening test been obtained. The data on the presence of antibodies to the hepatitis B surface and core antigens can be helpful in identifying children with chronic hepatitis B, who are assuredly in need of careful follow-up because of the increased risk of hepatocellular carcinoma and cirrhosis. Any child who is positive for hepatitis B surface antigen also needs a determination of hepatic transaminases. Whenever an adopted child tests positive for the hepatitis B surface antigen—whether the diagnosis be acute hepatitis B, chronic hepatitis B, or simple carrier status—household contacts should be immunized because they are at increased risk of contracting this disorder. A more detailed discussion of these issues can be found in the excellent paper by Hershow et al.[8]

Intestinal Parasites

The diagnosis and treatment of intestinal parasites are important adjuncts to nutritional well-being. Although intestinal parasites rarely appear in infants adopted from Korean foster homes, these disorders are common in Indian and Latin American children. We therefore recommend repeated stool examination on any child who has received treatment for a parasitic infection, on ambulatory children who have been abandoned before placement in a nursery or orphanage, and on any child with appropriate symptoms, such as bloating, diarrhea, or weight loss. While we do not routinely recommend small-bowel sampling for the diagnosis of *Giardia*, because most major infestations will have cysts or trophozoites in the stool,[5] a more directed approach may be necessary in symptomatic children in whom repeated stool examinations have failed to yield a pathogen. In addition, symptomatic children, particularly those from Indian nurseries, should have stool cultures for *Salmonella, Shigella, Campylobacter,* and *Yersinia*. It is best for the physician to determine the requirements of the local laboratory before submitting stool specimens.

Tuberculosis

The American Academy of Pediatrics recommends that the Mantoux intradermal skin test be used for screening

children from countries where tuberculosis is endemic.[10(p377)] The tine test is inadequate for screening adopted children from abroad. Moreover, we recommend the placement of a *Candida* control, because the nutritional status of some children may render them anergic and invalidate a negative Mantoux derivative test. Because of concern regarding efficacy, BCG vaccine is rarely given to international adoptees, and its administration is typically recorded on the health care summary from the country of origin. Because studies in the literature have documented waning of the hypersensitivity response to BCG within 1 year after its administration, placement of a Mantoux skin test more than 1 year after the BCG vaccination should not result in a false-positive test.[11] Thus, the physician should not defer the application of a Mantoux skin test, especially in a symptomatic child, if BCG vaccine was administered more than 1 year before the child's physical examination.

CMV

Cytomegalovirus excretion was the most common medical diagnosis in our clinic, with approximately one third of all children excreting this virus. This is not an unexpected finding, since many women of childbearing age in India and other parts of Asia excrete CMV on a recurrent basis.[12] Without adequate birth histories, however, the physician is at a disadvantage in differentiating a child with perinatal acquisition of CMV, who is at no risk of secondary complications, from the child with asymptomatic congenital CMV, who may be at risk for intellectual deficits or hearing loss later in life.[12]

By far the most important reason to screen for CMV, however, is the immune status of the adoptive mother. In North America, almost 50% of the women of childbearing age in middle and upper income groups are not immune to CMV[13]; hence, introduction of a CMV-excreting child into such a home may result in the acquisition of primary infection by the adoptive mother. If acquisition of CMV occurs during a biologic pregnancy, the adoptive mother may then transmit the virus to her fetus, with risk of the severe sequelae of congenital CMV. For this reason we recommend urine culture for CMV in our internationally adopted children. When CMV is cultured from a child's urine we advise the adoptive mother to have a serologic test for immunity to CMV. If she is not immune, she is thoroughly counseled regarding CMV transmission by urine and oral secretions and is advised on careful personal hygiene when performing diaper changes, disposing of diapers, or handling toys and other objects contaminated with saliva.[14,15]

Unfortunately, no preventive vaccine for CMV exists; hence, such hygienic practices are the only means available to limit the spread of CMV to susceptible women of childbearing age. An alternative to culturing the child's urine is determining the immune status of the adoptive mother. However, because only one third of our population was excreting CMV, a great many mothers would be tested unnecessarily.

Whichever method of testing is used, the physician should be sure to counsel the adoptive mother regarding the possibility of CMV, its modes of transmission, and its possible effects on a biologic pregnancy. Each of our mothers is prospectively counseled at the first clinic visit; if the child subsequently proves to be excreting CMV, the counseling is repeated. We find that this approach alleviates unnecessary fears and questions regarding CMV, while at the same time potentially mitigates the risk of CMV acquisition in pregnancy.

AIDS

Prominent among the screening tests that we do not routinely recommend is HIV testing. Figures from the World Health Organization continue to show that India, Korea, and most Central and South American countries have as yet little detectable risk of AIDS.[16] Cultural practices, such as the spread of prostitution and intravenous drug use, may change these figures in the future, but as yet no reason exists to recommend routine AIDS screening in these children. Countries with a high prevalence of AIDS include Brazil, Venezuela, Haiti, Honduras, and tropical African nations, in addition to the United States, but in 1987 children from these nations comprised only 3% of the orphans admitted to the United States.[3] Children adopted from these countries should have routine HIV screening.

Immunizations

Few children have been appropriately immunized before their arrival in the United States. Immunizations should begin immediately, according to the recommendations of the American Academy of Pediatrics.[10(pp697-706)]

Other Medical Considerations

Because visual defects can be difficult to identify on physical examination, all children should have a slit-lamp and funduscopic examination by an ophthalmologist within the first weeks after their arrival. Premature infants, especially, should be evaluated due to their inherent risk of retinopathy of prematurity, and the potential for effective surgical therapy should this condition be diagnosed.[17]

Hearing deficits in international adoptees are common. It is not unusual to see chronic draining ears, untreated tympanic perforations, and auditory sequelae in these children; hence, auditory screening, again within the first few weeks of arrival, is an important adjunct to preventive health care maintenance.

Physicians should also remember to avail themselves of state-supported newborn screening tests. While some of these screening tests may be inappropriate considering the age and nationality of these adopted children, others, such as those for hemoglobinopathies, may yield important results. Hemoglobin electrophoresis, though not routinely recommended, should be considered in any child with a hypochromic microcytic anemia, because hemoglobin E is common in children from Southeast Asia, while hemoglobin SS or S-thal may occur in children of mixed parentage from India, Central America, or South America.[18] Screening for glucose-6-phosphate dehydrogenase deficiency should also be considered in children of Mediterranean or African origin, in whom sulfa-containing antibiotics are to be administered.

Dental health is often overlooked in toddlers and older children. Many international adoptees have never brushed their teeth let alone seen a dentist. Therefore, oral health is often poor and extensive restorative work is often required to save or prevent damage to the child's permanent teeth. Physicians

should encourage parents to bring older children to their dentist within the first month after their arrival.

Day-care Considerations

One of the most common concerns that arises from the medical evaluation is the possibility of a child's exclusion from day-care. Abundant medical evidence shows that the child who is hepatitis B surface–antigen positive should not be excluded from day-care; medical and legal precedents concur that the child excreting CMV need not be excluded from day-care. Adoptive parents may be provided with two excellent articles on the subject.[8,19] In addition, appropriate counseling by the physician with the adoptive family and any day-care providers typically serves to alleviate problems that might otherwise arise. A reasoned and rational explanation of medical risk, as well as the knowledge that approximately one third of American children in day-care are also excreting CMV,[20,21] is the physician's best approach to this issue.

Circumcision

Adoptive parents frequently seek the physician's advice regarding circumcision of male adoptees and consideration of this issue should include the status of males in the adoptive family, cultural practices in the adoptee's country of origin, the emerging evidence that uncircumcised male infants may be more prone to urinary tract infection,[22] and the need for general anesthesia for circumcision performed after infancy. Well-informed adoptive parents can typically reach a satisfactory decision on this issue with appropriate physician guidance.

Developmental Assessment

An accurate developmental assessment at the first screening visit can be a great boon to physicians and parents alike, because concerns about the adoptive child's intellectual functioning are often of paramount importance in the first few weeks after his or her arrival. Our experience is most reassuring in this regard; 31 of the 48 children we examined were developmentally appropriate in tone, reflexes, gross motor milestones, fine motor development, and socialization.[7] Approximately 10% of our children showed isolated gross motor delay. Many of these children were nutritionally deprived and readily attained gross motor milestones when sufficient caloric intake was provided and muscle mass was attained. Despite their excellent nutritional status, Korean infants sometimes seem to be delayed in gross motor activities simply because, as the focus of attention in their Korean foster homes, they were rarely encouraged to sit or to reach. These motor milestones were readily attained when the infant was stimulated in his or her new home.

Seven children required interventional therapy. In another 10 children, instruction of parents in appropriate stimulatory maneuvers or entry of parent and child into a mother-infant stimulation program overcame the problem. Once again, the adoptive child will perform best after being acclimated to the family. Therefore, we recommend that the developmental examination be deferred until the child has been in the new home for 1 to 2 weeks.

As the true age of an older child may be unknown, parents may request developmental assessment as part of a medical evaluation to help determine the child's correct grade placement in school. As noted earlier, determining a child's actual age may be difficult as many of the traditional physical and roentgenographic parameters that are used may be altered by the conditions under which the child lived before arriving in the United States. Our belief is that psychometric testing may also be invalid for these children, especially if performed soon after their arrival. Concentrating on placing the child in an educational environment that considers his or her stage of physical development, socialization skills, and emotional stability often makes determination of actual chronologic age a moot issue.

Adjustment Problems

All international adoptees, infants as well as older children, may experience transient medical or emotional problems during adjustment to their new family situation. Sleep disturbances, malaise without fever, abdominal pain, and school avoidance may all be observed. We have not found highly unusual, esoteric, or geographic diseases to be the causes of such symptoms. Except for extremely disruptive or dangerous behavior or incapacitating physical symptoms, parents may need to be initially deterred from expensive or exhaustive medical evaluations, and encouraged to seek individual or family counseling only if such concerns persist.

Children adopted beyond the toddler stage frequently exhibit a variety of transitional behaviors that are somewhat more bewildering to their adoptive parents. By and large they involve "survival" types of behavior adopted by the child during periods of abandonment or neglect. Preoccupation with food is one of the most common types of unusual behavior observed in older adoptees. This may involve constantly thinking about food, worrying that the parents have enough food available, constant hunger, and even food hoarding. Once the child is reassured that he or she will not be hungry, this behavior usually resolves. Other more distressing types of behavior such as stealing, excessive physical violence, and precocious sexual behavior can also be understood if one considers the living conditions once forced on these children. However, these types of problems may require immediate professional intervention to protect the child's and family's safety and prevent the dissolution of the placement.

Long-term Care for the International Adoptee

As noted previously, the arrival of an adopted child from abroad into his or her adoptive family is only the beginning of a lifelong commitment by the adoptive parents to raise a child from a different culture. While on the whole this is a joyful duty, problems do exist and should be anticipated. Not only must the family address the issues inherent in any adoption, they must also be aware that their child and they themselves may be discriminated against because of their child's skin color, that their child will be the victim of racial stereotyping (eg, Korean math "whizzes"), that friends and their extended family may not readily embrace their child, and that they may be viewed as being a "second-class" or not a "real" family.

Cultural issues become important as the child approaches adolescence. De-

fining one's identity during this critical stage of development is difficult enough without the added burden of being distinctly different in many aspects from one's peers. The desire to establish contact with one's biologic family, commonly observed in adolescent adoptees, is made more difficult if not impossible by the circumstances surrounding international adoption. Therefore, it is not uncommon for parents to seek their physician's guidance when their "perfect child" becomes a "perfect terror" as they try to deal with these identity issues.

Space does not permit a full discussion of these issues; indeed, in some instances professional psychiatric or psychologic assistance may be necessary. However, the physician may be able to foster this process early in the child's life by encouraging adoptive parents to become involved with local adoptive parent support groups. Some of these groups are an outgrowth of agency services, while others are organized according to the child's country of origin. Not only do these groups provide the opportunity for children to socialize with their peers and learn to appreciate the culture from which they came, but parents can share experiences and solutions for problems that they share. As with anything in the practice of pediatrics, preventive care is well rewarded. A list of parent support groups as well as US agencies involved with international adoption can be obtained by writing to OURS, Inc, Suite 203, 3307 Hwy 100 N, Minneapolis, MN 55422.

CONCLUSION

In summary, we have found that caring for adopted children from abroad can be one of the highlights of pediatric practice. Not only are the children delightful, but one could scarcely find more devoted or motivated parents. These children and their families, however, do require special consideration that is somewhat different from that given to our US-born patients and their families. Physicians who spend the time to become acquainted with the process of international adoption and the medical problems commonly seen in this group of children will reap enormous personal and professional satisfaction as they help to enhance the health and well-being of these unique children and their families.

References

1. Mosher WD. Infertility: Why business is booming. *Am Demographics.* 1987;9:42-43.
2. Kaunitz AM, Grimes DA, Kaunitz KK. A physician's guide to adoption. *JAMA.* 1987;258:3537-3541.
3. *Immigrant Orphans Admitted to the United States by Country of Origin or Region of Birth 1978-1987.* Washington, DC: US Dept of Justice, Immigration and Naturalization Service.
4. Smith LM. Babies from abroad. *Am Demographics.* 1988;10:38-56.
5. Addendum to *Guidelines for Medical Examination of Aliens in the United States, June 1985 and Supplement, February 1987: Instructions for Substituting Human Immunodeficiency Virus (HIV) Infection for AIDS as an Excludable Health Condition and Incorporating Serologic Testing for HIV in the Medical Examination of Aliens.* Washington, DC: US Dept of Justice, Immigration and Naturalization Service, November 18, 1987.
6. Jenista JA, Chapman D. Medical problems of foreign-born adopted children. *AJDC.* 1987; 141:298-302.
7. Hostetter MK, Iverson S, Dole K, Johnson DE. Unsuspected infectious diseases and other medical diagnoses in the evaluation of internationally adopted children. *Pediatrics.* In press.
8. Hershow RC, Hadler SC, Kane MA. Adoption of children from countries with endemic hepatitis B: transmission risks and medical issues. *Pediatr Infect Dis J.* 1987;6:431-437.
9. Pickering LK, Woodward WE, DuPont HL, Sullivan P: Occurrence of *Giardia lamblia* in children in day care centers. *J Pediatr.* 1984;104:522-526.
10. American Academy of Pediatrics. *Report of the Committee on Infectious Diseases.* Elk Grove, Ill: American Academy of Pediatrics; 1986:377.
11. Lifschitz M. The value of the tuberculin skin test as a screening test for tuberculosis among BCG-vaccinated children. *Pediatrics.* 1965;36:624-627.
12. Overall JC Jr. Viral infections of the fetus and neonate. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases.* Philadelphia, Pa: WB Saunders Co; 1986:977-981.
13. Stagno S, Pass RF, Dworsky ME, et al. Congenital cytomegalovirus infections: the relative importance of primary and recurrent maternal infection. *N Engl J Med.* 1982;306:945-949.
14. Hanshaw JB. Cytomegalovirus infections. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases.* Philadelphia, Pa: WB Saunders Co;1986:1558-1566.
15. Pomeroy C, Englund JA. Cytomegalovirus: epidemiology and infection control. *Am J Infect Control.* 1987;15:107-119.
16. Mann JM, Chin J, Piot P, Quinn T. The international epidemiology of AIDS. *Sci Am.* 1988;259:82-89.
17. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. *Pediatrics.* 1988;81:697-706.
18. Morizon CM, Fairbanks VF, Burgert EO Jr, Sutherland JE, Elliott SC. Hematologic genetic disorders among Southeast Asian refugees. *Am J Hematol.* 1985;19:27-36.
19. Blackman JA, Appel BR. Epidemiologic and legal considerations in the exclusion of children with acquired immunodeficiency syndrome, cytomegalovirus, or herpes simplex virus infection from group day care. *Pediatr Infect Dis J.* 1987;6:1011-1015.
20. Adler SP. Molecular epidemiology of cytomegalovirus: viral transmission among children attending a day care center, their parents, and caretakers. *J Pediatr.* 1988;112:366-372.
21. Murph JR, Bale JF Jr. Natural history of acquired cytomegalovirus infection among children in group day care. *AJDC.* 1988;142:843-846.
22. Wisell TE, Smith FR, Bass JW. Decreased incidence of urinary tract infections in circumcised male infants. *Pediatrics.* 1985;75:901-903.

In Other AMA Journals

JAMA

Juvenile Glaucoma, Race, and Refraction

D. Lotufo; R. Ritch; L. Szmyd, Jr; J. E. Burris (*JAMA.* 1989;261:249)

Articles

Does Maternal Cigarette Smoking During Pregnancy Cause Cleft Lip and Palate in Offspring?

Muin J. Khoury, MD, PhD; Marco Gomez-Farias, MD, MPH; Joseph Mulinare, MD, MSPH

• To investigate the relationship between maternal cigarette smoking and the risk of oral clefts in offspring, we examined data from the Atlanta Birth Defects Case-Control Study, which included 238 cases of cleft lip with or without cleft palate and 107 cases of cleft palate ascertained by the Metropolitan Atlanta Congenital Defects Program from 1968 through 1980. In all, 2809 infants who served as controls were frequency matched to cases by race, period of birth, and hospital of birth. Maternal periconceptional exposures to smoking were investigated through use of a structured questionnaire. Smoking exposure was defined as reported maternal smoking during the periconceptional period (from 3 months before conception to 3 months after pregnancy began). Offspring of smoking mothers were 1.6 and 2.0 times more likely than offspring of nonsmoking mothers to have isolated cleft lip with or without cleft palate and cleft palate, respectively. On the other hand, offspring of smoking mothers were not at increased risk of having cleft palate or cleft lip with or without cleft palate that are associated with other defects. Adjustment for potential confounding variables did not alter these results. A relatively modest effect of smoking may be explained by the presence of underlying etiologic heterogenity in oral clefts and differential susceptibility to smoking. Because of the inconsistencies in the literature on the relationship between smoking and oral clefts, these results suggest the need to refine oral clefts into more homogeneous subgroups in epidemiologic studies of these defects.

(*AJDC*. 1989;143:333-337)

The relationship between smoking during pregnancy and a variety of adverse reproductive outcomes has been established.[1] Such outcomes include spontaneous abortion, prematurity, and intrauterine growth retardation.[1] However, a teratogenic effect of smoking has not been consistently found in epidemiologic studies.[1,2] More specifically, several investigators have found an increased risk of oral clefts in offspring of women who smoked during pregnancy,[3-6] although others did not confirm such a relationship.[7-10] In a population-based study of smoking and clefts, Khoury et al[3] found an association between cigarette smoking and the risk of isolated cleft lip and cleft palate. In most previous studies, however, cleft cases have not been separated on the basis of presence or absence of associated defects.[4,5,7-10] If cigarette smoking is related to a subgroup of cases of oral clefts, then lumping all cleft cases in an epidemiologic study may obscure the finding of a true association. Because the presence of associated defects in an infant with a cleft can point to an underlying etiologic heterogeneity,[11] it is important to examine the relationship between smoking and subgroups of clefts on the basis of the type of cleft (cleft lip with or without cleft palate [CLP] or cleft palate [CP], presence of other defects, and presence of syndromes of recognized etiology.

In our present study, we used data from the population-based Atlanta Birth Defects Case-Control Study to further evaluate the association between maternal smoking and the risk of cleft lip and palate, specifically according to the patterns of associated defects in addition to the oral cleft. The results of this study are discussed in the context of prior investigations and the possible teratogenicity of maternal cigarette smoking.

SUBJECTS AND METHODS

Study Population

Data used in this study were part of a large population-based case-control study of birth defects in which a variety of risk factors for birth defects were evaluated. The study design and methods of analysis have been described in detail elsewhere.[12,13] Briefly, the Atlanta Birth Defect Case-Control Study included infants with major structural birth defects diagnosed in the first year of life, born from 1968 through 1980 to residents of metropolitan Atlanta. Cases were actively ascertained from local Atlanta hospitals by Centers for Disease Control staff as part of the routine surveillance system (Metropolitan Atlanta Congenital Defects Program[14]). Multiple sources were used to identify cases

Accepted for publication November 19, 1988.

From the Birth Defects and Genetic Diseases Branch, Division of Birth Defects and Developmental Disabilities, Center for Environmental Health and Injury Control, Centers for Disease Control, Public Health Service, US Department of Health and Human Services (Drs Khoury and Mulinare), and the Department of Community Health, Emory University School of Medicine (Dr Gomez-Farias), Atlanta, Ga

Reprint requests to Centers for Disease Control, Division of Birth Defects and Developmental Disabilities, Atlanta, GA 30333 (Dr Khoury).

Table 1.—Oral Clefts in Cases by Patterns of Associated Anomalies, Atlanta Birth Defects Case-Control Study, 1968-1980

	No. (%) of Infants	
Type of Cleft	Cleft Lip and/or Cleft Palate (n=238)	Cleft Palate (n=107)
Isolated	172 (72.3)	56 (52.3)
Multiples	52 (21.8)	38 (35.5)
Syndromes	14 (5.9)	13 (12.2)

and their patterns of associated defects, including review of hospital medical records, autopsy results, specialty clinics, cytogenetic laboratories, and vital records. Controls were chosen from among the 323 421 live births that occurred during the same period to women who were residents of metropolitan Atlanta. Controls were frequency matched to infants by period of birth, race, and hospital of birth. In all, 4929 mothers of infants with birth defects and 3029 mothers of infants who served as controls completed telephone interviews (70% participation rate), which included questions concerning a variety of medical, demographic, and periconceptional exposures.[12]

Defects and Classification

Oral cleft cases used in the analysis include the following two categories: CLP (238 cases) and CP without cleft lip (107 cases). The two categories were chosen because of well-known epidemiologic and genetic differences reported in previous studies.[15-18] Also, each category of cases was classified into three groups depending on patterns of associated defects according to the recommendations of Spranger et al,[11] including (1) isolated: the cleft is the only major defect (also included under isolated are cases that have minor anomalies or defects that are secondary to the cleft, such as the Pierre Robin sequence); (2) multiples: cleft cases with other major defects that are not part of a recognized syndrome; and (3) syndromes: cleft cases that have other major defects that are part of a recognized syndrome (chromosomal, mendelian, or known teratogen). Analyses were performed on subjects with CLP and CP, total, isolated, and multiple categories, separately. Syndromic cleft cases were excluded from the analysis of multiple defects.

Definition of Smoking Exposure

During the interview, mothers of infants with birth defects and mothers of infants who served as controls were asked whether they smoked cigarettes at any time during the periconceptional period (including 3 months before conception to 3 months after the pregnancy began). They were also asked about the specific timing of smoking during these 6 months, the number of cigarettes smoked per day, and whether the pattern of smoking changed during pregnancy. Because less than 10% of women reported a change in smoking patterns during these months, we defined as exposed all mothers who reported smoking any time during the periconceptional period, 3 months before conception to 3 months after pregnancy began. In further analyses, we examined four levels of smoking "dose": (nonsmokers, less than 15 cigarettes per day, 15 to 24 cigarettes per day, and more than 25 cigarettes per day).

Table 2.—Maternal Demographic and Exposure Characteristics of Oral Clefts in Cases and Controls, Atlanta Birth Defects Case-Control Study, 1968-1980*

Maternal Characteristic	No. (%) Cleft Lip and/or Cleft Palate (n=238)	Cleft Palate (n=107)	Controls (n=2809)
Race			
White	204 (85.7)	78 (72.9)	2199 (78.3)
Nonwhite	34 (14.3)	29 (27.1)	610 (21.7)
Maternal education			
Grammar school	34 (14.3)	24 (22.4)	444 (15.8)
High school	162 (68.1)	63 (58.9)	1812 (64.5)
College	42 (17.7)	20 (18.7)	553 (19.7)
Birth period			
Jan 1969-Apr 1972	80 (33.6)	26 (24.3)	822 (29.3)
May 1972-Aug 1976	88 (37.0)	41 (38.3)	936 (33.3)
Sep 1976-Dec 1980	70 (29.4)	40 (37.4)	1051 (37.4)
Maternal age, y			
<20	31 (13.0)	12 (11.2)	308 (11.0)
20-24	75 (31.5)	41 (38.3)	846 (30.1)
25-29	78 (32.8)	33 (30.8)	1008 (35.9)
30-34	43 (18.1)	17 (15.9)	507 (18.1)
≥35	11 (4.6)	4 (3.7)	138 (4.9)
Alcohol use			
No	113 (47.9)	64 (59.8)	1387 (49.5)
Yes	123 (52.1)	43 (40.2)	1414 (50.5)
Tranquilizer use			
No	216 (92.3)	97 (91.5)	2670 (95.6)
Yes	18 (7.7)	9 (8.5)	122 (4.4)
Birth control pill use			
No	186 (78.5)	88 (82.2)	2191 (78.3)
Yes	51 (21.5)	19 (17.8)	608 (21.7)
No. of previous births			
0	110 (46.2)	46 (43.0)	1194 (42.5)
1-3	124 (52.1)	55 (51.4)	1505 (53.6)
≥4	4 (1.7)	6 (5.6)	110 (3.9)
Previous unproductive pregnancies			
No	188 (79.0)	84 (78.5)	2246 (80.0)
Yes	50 (21.0)	23 (21.5)	563 (20.0)
Spermicide use			
No	206 (86.5)	91 (85.1)	2340 (83.5)
Yes	32 (13.5)	16 (14.9)	463 (16.5)
Pregnancy planned			
No	121 (50.8)	65 (60.8)	1448 (51.6)
Yes	117 (49.2)	42 (39.2)	1359 (48.4)
Vitamin use			
No	108 (46.7)	44 (41.1)	1083 (39.3)
Yes	123 (53.3)	63 (58.9)	1671 (60.7)

*Missing data for cases and controls were excluded.

Methods of Analysis

We used conditional logistic regression methods to examine the relationship between smoking and clefts (and subgroups) and to adjust for potential confounding variables. As described elsewhere,[12] the three design variables (race, white and others; period of birth; and 20 hospitals of birth) were used to create 120 strata for analysis. In addition to the design variables, adjustment included other variables that were shown to be related to either smoking and/or clefts. These included: maternal age (under 20, 20 to 24, 25 to 29, 30 to 34, and 35 years or older); maternal education (elementary, high school, college); previous unproductive pregnancy (yes/no); whether the pregnancy was planned or not; and certain exposures during the periconceptional period, including, alco-

Table 3.—Crude and Adjusted Odds Ratios of Maternal Smoking Associated With Oral Clefts, by Type of Cleft, and Associated Anomalies, Atlanta Birth Defects Case-Control Study, 1968-1980*

	All Cases	Isolated	Multiples
Cleft lip and/or cleft palate (n=238)			
Maternal smokers, %	42.0	44.2	36.5
Crude odds ratio (95% CI)	1.48 (1.13-1.95)	1.59 (1.16-2.19)	1.17 (0.65-2.10)
Adjusted odds ratio† (95% CI)	1.47 (1.09-1.97)	1.55 (1.10-2.18)	1.30 (0.69-2.44)
Cleft palate (n=107)			
Maternal smokers, %	38.3	46.4	26.3
Crude odds ratio (95% CI)	1.39 (0.93-2.09)	1.87 (1.08-3.23)	0.88 (0.42-1.84)
Adjusted odds ratio† (95% CI)	1.50 (0.97-2.32)	1.96 (1.10-3.50)	1.01 (0.45-2.26)

*CI indicates confidence interval.
†Adjusted for maternal age, education, alcohol consumption, birth control pill use, tranquilizer use, spermicide use, pregnancy planning status, previous unproductive pregnancies, and the design variables (race, period of birth, and hospital of birth).

Table 4.—Odds Ratios of Smoking With Isolated Oral Clefts, by Number of Cigarettes per Day, Atlanta Birth Defects Case-Control Study, 1968-1980*

	Cleft Lip and/or Cleft Palate		Cleft Palate	
No. of Cigarettes/d	%	Odds Ratio (95% CI)	%	Odds Ratio (95% CI)
≤14	18.6	1.56 (1.02-2.38)	20.8	1.82 (0.89-3.72)
15-24	18.0	1.55 (1.00-2.40)	18.9	1.87 (0.88-3.98)
≥25	6.6	1.87 (0.95-3.65)	3.8	1.08 (0.25-4.68)

*CI indicates confidence interval.

hol use, use of oral contraceptives, use of tranquilizers, and use of spermicides (all categorized as yes/no variables). Adjusted estimates of the odds ratios of smoking, and their 95% confidence intervals, were obtained by using the antilogs of the regression coefficients and their SEs estimated by the model. A lower bound odds ratio estimate larger than unity was considered as statistically significant.

RESULTS

Classification of Oral Cleft Cases

As shown in Table 1, 238 cases of CLP and 107 cases of CP were available for the analysis. Of these, 72.3% of CLP (172 cases) and 52.3% of CP (56 cases) were isolated defects, while 21.8% of CLP (52 cases) and 35.5% (38 cases) of CP had other defects. There were 14 cases of CLP and 13 cases of CP that were part of recognized syndromes.

Characteristics of Cases and Controls

Table 2 compares maternal demographic and exposure characteristics in infants with birth defects with those in controls. There were no substantial differences between subjects with CLP or CP and controls with respect to the distribution of maternal age, education, number of previous births, previous unproductive pregnancies, alcohol use, use of oral contraceptives, spermicide use, and pregnancy planning status. On the other hand, subjects with CLP were more likely to be white than subjects with CP, and controls (86% vs 73% and 78%) were more likely to be born in earlier years (in period 1, 34% vs 24% and 29%) and less likely to have mothers who used vitamins during the periconceptional period (53% vs 59% and 61%). Also, compared with controls, mothers of infants with CLP and mothers of infants with CP were more likely to report the use of tranquilizers in the periconceptional period (about 8% vs 4%).

Crude and Adjusted Effects of Maternal Cigarette Smoking

Table 3 shows crude and adjusted odds ratios of maternal cigarette smoking as related to the risk of CLP, CP, and their subgroups (isolated and multiples). Multivariate adjustment did not appreciably change the magnitude of the crude odds ratio. If all cleft cases are combined, maternal smoking was not a significant risk factor for both CLP and CP (adjusted odds ratios of 1.47 and 1.50, respectively, with confidence intervals overlapping one). On the other hand, when clefts are subdivided into isolated and multiples, only isolated CLP and CP were statistically significantly associated with smoking (adjusted odds ratios of 1.55 and 1.96, respectively), while multiples were not associated with smoking (adjusted odds ratios of 1.30 and 1.01, respectively).

Dose-Response Analysis of Smoking and Clefts

Table 4 shows the odds ratios of smoking and isolated CLP and CP by number of cigarettes smoked per day. Three levels are shown: 14 or fewer, 15 to 24, and 25 or more cigarettes per day. Because the crude and adjusted odds ratios were very close, only crude odds ratios are presented herein. As can be shown, for CLP, there is a suggestive dose-response trend with odds ratios of 1.56, 1.55, and 1.87. This trend was not statistically significant, however (by applying the Mantel test for trend). For CP, there is no apparent dose-response effect of smoking.

COMMENT

In this population-based case-control study of maternal smoking and the risk of oral clefts in the offspring, we found that mothers who smoked in the periconceptional period had a statistically significantly elevated risk of isolated cleft lip and palate in their infants than nonsmoking mothers. The magnitude of the relative risk is in the range of 1.5 to 2. No association was found between smoking and oral clefts associated with other defects.

To interpret these findings, we need to recognize some possible limitations of this study and of observational studies in general. Also, one should consider the results of this investigation in the light of previously conducted epidemiologic studies of maternal smoking and oral clefts. First, the association found here could be due to unmeasured confounding factors. We attempted to consider and adjust for all available factors that

Table 5.—Maternal Cigarette Smoking and Risk of Oral Clefts in Offspring: Review of Some Published Studies*

Source, y	Population	Type of Study	No. of Cleft Cases	Odds Ratio	Attributable Fraction, %	Proportion Susceptibles, %
Present study	Metropolitan Atlanta Congenital Defects Program	Case-control	CLP: 238 CP: 107	CLP: 1.5 CP: 1.5	CLP: 13 CP: 13	0.04 0.02
Khoury et al,[3] 1987	Maryland Birth Defects Registry	Case-control	CLP: 27 CP: 26	CLP: 2.6 CP: 2.4	CLP: 34 CP: 31	0.05 0.05
Shiono et al,[7] 1986	Kaiser-Permanente Study	Cohort	CLP: 32 CP: 24	CLP: 1.1 CP: 0.7	CLP: 3	0.01
Hemmink et al,[8] 1983	Finnish Register of Congenital Defects (1967-1977)	Case-control	. . .	All: 1.25	All: 4	0.04
Ericson et al,[4] 1979	Swedish Delivery Records	Case-control	CLP: 51 CP: 17	CLP: 2.7 CP: 4.6	CLP: 43 CP: 61 minimum All: 22	0.10 0.07 0.08
Kelsey et al,[19] 1978	Several hospitals in Connecticut	Case-control	All: 40	All: 1.0 (1-20/d) All: 1.7 (21+/d)	All: 3	0.11
Evans et al,[10] 1975	Cardiff Birth Survey (1965-1976)	Cohort	All: 111	All: 1.3	All: 11	0.04
Saxen,[9] 1975	Finnish Register (1972-1973)	Case-control	All: 194	All: 1.2	All: 2	0.04
Saxen,[5] 1974	Finnish Register (1967-1971)	Case-control	All: 599	All: 2.3	All: 6	0.19
Andrews and McGarry,[6] 1972	Cardiff Birth Survey (1965-1968)	Cohort	All: 30	All: 2.4	All: 38	0.15

*CLP indicates cleft lip with or without cleft palate; CP, cleft palate; and all, all clefts.

may be associated with smoking and/or clefts in our multivariate analysis. Second, the findings could be due to other biases frequently seen in case-control studies, notably selection and recall bias. It is difficult to explain the association on the basis of these types of biases, because this is a population-based study. Also, when cases of birth defects other than oral clefts were used as a control group, the odds ratios relating maternal smoking and clefts did not change appreciably, which underlines a specific association between smoking and isolated clefts. Third, further refinement of cleft cases by side of lesion and severity could not be done because such information was not always collected. Finally, this association could be a chance finding (α error). However, this is an unlikely possibility because this analysis was prompted by the finding of a similar association between smoking and isolated clefts in another population.[3]

How do our findings compare with those of previously published studies of smoking and oral clefts? Table 5 shows a summary of findings from our study and prior investigations.[3-10,19] It is important to keep in mind that these studies have several differences in design (case-control, cohort), in the sample sizes of cleft cases available, in the measurement and adjustment for other potential confounding factors, in the definition of the smoking exposure variable, and in the classification of clefts by patterns of associated defects. All of these factors may affect comparability of the results. In fact, except in the studies of Saxen[5] and Khoury et al,[3] cleft cases were not subdivided into isolated and multiple defects in any of the other studies noted. Moreover, in several studies, clefts have not even been subdivided into CLP and CP, despite the known epidemiologic and genetic differences between the two entities. In the study of Khoury et al,[3] a similar finding of smoking and isolated CLP and CP is reported. In Saxen's study,[5] an association between smoking and both isolated and multiple clefts is reported. However, the magnitudes of the odds ratio estimates were not reported for each group.

When oral clefts are considered as a group regardless of the presence or absence of associated defects, point estimates of odds ratios ranged between 1 and 3 in various studies. Statistical power was not adequate in some of these studies to show a statistically significant finding. Thus, the results of most studies indicate that the magnitude of the relative risk of clefts associated with cigarette smoking is relatively low. The interpretation of low (but statistically significant) relative risks has always posed some difficulties in epidemiologic investigations. On the one hand, low relative risks could be due to unmeasured confounding factors or other forms of biases inherent in observational studies. On the other hand, low relative risks may not be unexpected in the presence of etiologic heterogeneity and multiple-factor interaction.[20-22]

In a disease that is etiologically heterogeneous, common exposures (such as smoking) are often associated with low relative risks that are difficult to measure in epidemiologic studies.[22] If smoking is associated with only isolated clefts, then lumping all cases together may dilute the magnitude of the association. In addition to relative risk measures, it is important to assess the magnitude of the attributable risk or fraction. This epidemiologic concept re-

fers to the proportion of cases in a population that can be attributed to a specific causal factor[20] By using data from the published studies, we have computed the attributable fraction of oral clefts associated with smoking. These estimates provide only a crude measure of the contribution of smoking to oral clefts in different populations. As shown in Table 5, because the prevalence of smoking in these populations was relatively high (mostly between 10% and 35%), a low relative risk may translate into a relatively large attributable fraction. The estimates we obtained were between 2% and 60%, with half the studies showing an attributable fraction of 10% or more. When only isolated clefts are considered, we obtain an estimate of attributable fraction in this study of 16% for CLP and 22% for CP. Thus, if the relationship between smoking and isolated clefts is causal, smoking probably accounts for about 20% of such cases in this population.

Another factor associated with low relative risks in epidemiologic studies is differential susceptibility to the effects of smoking in the population (interaction of smoking with other factors). If the association between smoking and clefts is causal, one can compute a measure of the proportion of susceptibles to smoking. Khoury et al[23] have derived several measures of the proportion of susceptibles to an exposure, which is the proportion of persons who, if exposed, would contract disease from exposure, in the absence of other causal factors. For rare diseases, such a proportion is very close to the risk difference between exposed and unexposed.[23] For example, Khoury et al estimated that about 20% of persons are susceptible to the induction of limb reduction defects by thalidomide, a potent human teratogen. We applied this concept to the smoking-cleft associations in this and other studies. As shown in Table 5, the proportion of persons who may be biologically susceptible to the induction of clefts by smoking was estimated to be low, in the range of 0.1% or less in most studies.

Thus, if maternal cigarette smoking has a pathogenetic role in the induction of clefts, it probably does so for a selected subgroup of oral clefts that will have to be characterized further, both clinically and pathogenetically. Also, a small fraction of the population at large may be biologically susceptible to a teratogenic effect of smoking. One possible clue to a differential susceptibility to birth defects in smokers comes from recent studies on the cytochrome P-450 system, a genetically determined enzyme system that plays a major role in the detoxification of chemicals and drugs.[24] Manchester and Jacoby[25] presented evidence of induction of placental cytochrome P-450 monooxygenase activity in response to maternal smoking. Subsequently, they found that among smokers, low placental monooxygenase activity was significantly correlated with the presence of birth defects in their offspring.[26] One explanation for this finding is that certain persons may be more susceptible to the teratogenic action, depending on their ability to detoxify chemicals found in cigarette smoke. Further studies need to be done on these initial findings to examine whether susceptibility to a possible teratogenic effect of smoking may be related to the cytochrome P-450 enzyme system.

In summary, maternal cigarette smoking was found to be a statistically significant risk factor for isolated cleft lip and palate in this population-based study. If the finding is not due to unmeasured confounding, it points to the importance of low relative risk estimates found in epidemiologic studies. A relatively modest effect of smoking may be explained by the presence of underlying etiologic heterogeneity in oral clefts and differential biologic susceptibility to the teratogenic effects of smoking.

The authors thank John Boring, PhD, for support, Kathleen Maloney and Johnny Hutchison for programming help, and Essie Fuller for preparation of the manuscript.

References

1. Werler MM, Pober BR, Holmes LB. Smoking and pregnancy. In: Sever JL, Brent RL, eds. *Teratogen Update: Environmentally Induced Birth Defects Risks*. New York, NY: Alan R. Liss Inc; 1986:131-139.
2. Schardein JL. *Chemically Induced Birth Defects*. New York, NY: Marcel Dekker Inc; 1985: 764-769.
3. Khoury MJ, Weinstein A, Panny S, et al. Maternal cigarette smoking and oral clefts: a population-based study. *Am J Public Health*. 1987; 77:623-625.
4. Ericson A, Kallen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. *Am J Obstet Gynecol*. 1979;135:348-351.
5. Saxen I. Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. *Int J Epidemiol*. 1974;3: 263-270.
6. Andrews J, McGarry JM. A community study of smoking in pregnancy. *J Obstet Gynaecol Br Common*. 1972;79:1057-1073.
7. Shiono PH, Klebanoff MA, Berendes HW. Congenital malformations and smoking during pregnancy. *Teratology* 1986;34:65-71.
8. Hemminki K. Mutanen P, Saloniemi I. Smoking and the occurrence of congenital malformations and spontaneous abortions: a multivariate analysis. *Am J Obstet Gynecol*. 1983;145:61-66.
9. Saxen I. Epidemiology of cleft lip and palate: an attempt to rule out chance correlations. *Br J Prev Med*. 1975;29:103-110.
10. Evans DR, Newcombe RG, Campbell H. Maternal smoking habits and congenital malformations: a population study. *Br Med J*. 1975;2:171-173.
11. Spranger J, Benirschke, Hall JG, et al. Errors of morphogenesis: concepts and terms. *J Pediatr*. 1982;100:160-165.
12. Erickson JD, Mulinare J, McClain PW, et al. *Vietnam Veterans' Risks for Fathering Babies With Birth Defects*. Atlanta, Ga: Centers for Disease Control; 1984.
13. Erickson JD, Mulinare J, McClain PW, et al. Vietnam veterans' risks for fathering babies with birth defects. *JAMA*. 1984;252:903-912.
14. Edmonds LD, Layde PM, James LM, et al. Congenital malformations surveillance: two American systems. *Int J Epidemiol*. 1981;10:247-252.
15. Fraser FC. The genetics of cleft lip and palate. *Am J Hum Genet*. 1970;22:336-352.
16. Emanuel I, Culver BH, Erickson JD, Guthrie B, Schuldberg D. The further epidemiologic differentiation of cleft lip and palate: a population study of clefts in King County, Washington, 1956-1965. *Teratology*. 1973;7:271-281.
17. Shprintzen RJ, Siegel-Sadewitz VL, Amato J, Goldberg RB. Anomalies associated with cleft lip, cleft palate or both. *Am J Med Genet*. 1985;20:585-595.
18. Moore KL. *The Developing human: Clinically Oriented Embryology*. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1982:206-213.
19. Kelsey JL, Dwyer T, Holford TR, Bracken MB. Maternal smoking and congenital malformations: an epidemiological study. *J Epidemiol Community Health*. 1978;32:102-107.
20. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little, Brown & Co Inc; 1986.
21. Weiss NF, Liff J. Accounting for the multicausal nature of disease in the design and analysis of epidemiologic studies. *Am J Epidemiol*. 1983; 117:14-18.
22. Khoury MJ, Stewart W, Beaty TH. The effect of genetic susceptibility on causal inference in epidemiologic studies. *Am J Epidemiol*. 1987; 126:561-567.
23. Khoury MJ, Flanders WD, Greenland S, Adams MJ. On the measurement of susceptibility in epidemiologic studies. *Am J Epidemiol*. 1989; 129:183-190.
24. Spielberg SP. Pharmacogenetics and the fetus. *N Engl J Med*. 1982;307:115-116.
25. Manchester DK, Jacoby EH. Resolution and reconstitution of human placental monooxygenase activity responsive to maternal cigarette smoking. *Dev Pharmacol Ther*. 1982;5:162-172.
26. Manchester DK, Jacoby EH. Decreased placental monooxygenase activity associated with birth defects. *Teratology*. 1984;30:31-37.

Recurrent Injuries in Schoolchildren

W. Thomas Boyce, MD, Sue Sobolewski, RN, MPH

• Past work identifying "accident-prone" children with disproportionate rates of injury has been based on clinical data gathered in office, clinic, or emergency department settings. To avoid the biases inherent in such designs, we studied recurrent injuries in a school district population, utilizing a prospective surveillance system to identify injuries meeting standardized criteria. During three school years we observed 54 874 students, ranging in age from 6 to 18 years, for recurrent injuries, which were defined as those occurring in a year in which two or more injuries were reported for the child. Five hundred seventy-three recurrently injured children (1% of the school district population) sustained 1405 injuries (17% of the overall injury experience), a proportion significantly but only slightly greater than that expected on the basis of chance alone (14%). Most recurrently injured children were injured in only a single year, with only 15 children sustaining injuries in all three study years. Age, sex, and type of school were significant correlates of recurrent injury rates, with junior high school students, boys, and students attending schools with alternative educational programs having the highest rates of injury recurrence. The findings indicate that (1) a small group of schoolchildren sustain a disproportionate share of the overall injury experience, (2) the majority of recurrently injured children experience only transient periods of enhanced injury risk, and (3) preventive strategies may benefit from investigation of developmental and social environmental factors that alter such risk.

(*AJDC* 1989;143:338-342)

In the United States and other countries of the industrialized world, injuries are the leading cause of morbidity and mortality for children over 1 year of age. Twenty-two million children are injured in the United States each year, a number representing one of every three children less than 17 years of age.[1-4] Use of the term *accident* has, in the past, suggested that injuries occur as random events, without pattern or predictability.[5,6] It is increasingly apparent, however, that injury occurrence is highly nonrandom and that rates of injuries vary markedly among demographic subgroups of children.[7,8] Excessive rates of injury have been documented, for example, among male children,[9-11] among children at certain high-risk ages,[12-16] and among children from families of lower socioeconomic status.[17] Recent work addressing the epidemiologic features of injuries has delineated complementary and interactive roles of host, agent, and environment in the causation of injury-related morbidity.[5,6,9-11]

While there is indisputable evidence of excessive injury rates among specific subgroups of children, questions regarding "injury proneness" among individual children remain disputed and unresolved. The concept of an enduring, personal predisposition to injuries originated in British studies of munitions factory workers during World War I,[18-20] with the observation that certain individuals sustained a disproportionate share of the overall industrial injury experience. Researchers concluded that injury liability was unevenly distributed within the worker population and that some workers were inherently more likely to incur injuries than others, a condition described as "accident proneness" by Farmer and Chambers.[21] The statistical interpretation of this observation has been repeatedly questioned,[20,22,23] but the concept of a personal predilection to injury has remained an active, although persistently debated, component of conventional medical wisdom.

It is perhaps in regard to the childhood years that the concept of injury proneness has been most widely and visibly promulgated. A number of investigators have approached the study of children's injuries by identifying and examining the characteristics of children with multiple, recurrent injuries.[24-32] Although some have dismissed injury proneness as a misinterpretation of statistical data,[18,20,22,23] others have upheld the concept, identifying both personal[16,29,32,33] and environmental[26,28] factors that seem to increase an individual child's liability to injury. The pediatrician's ability to summarize and objectively weigh evidence regarding the "injury-prone" child has been undermined by a variety of methodological shortcomings contained in past research. These shortcomings have included (1) small populations; (2) short sampling frames, typically covering periods of only weeks or months; (3) selection and reporting biases inherent in the use of emergency department and hospital data; and (4) nonstandardized criteria for defining and recording an injury event. We have therefore studied a large, representative population of school-age children over a three-year period, employing standardized reporting criteria to examine injury recurrences within a large, urban school district.

SUBJECTS AND METHODS

We employed the data collection methods of an ongoing, previously described[9] injury surveillance system that was established in a large, urban Arizona school district beginning in 1979. Data were collected during the three academic years between September and June, 1980 to 1983. No information was obtained on injuries occurring outside of school or during the summer months. The school district comprised 96 schools with a total attendance of 54 874 students representing a broad variety of income and racial groups. In brief, the surveillance system employed the use of self-coded reporting forms, completed by school nurses on all injuries meeting at least one of three criteria: (1) required a physician's care and/or major first aid; (2) resulted in an absence from school; or (3) resulted in restricted participation in competitive sports. Data collected on such injuries included the name, age, and sex of the child; the apparent cause of the injury; the location, time, and type of injury; and the

Accepted for publication Nov 25, 1988.

From the Division of Behavioral and Developmental Pediatrics, Department of Pediatrics, University of California, San Francisco (Dr Boyce), and the Tucson Unified School District (Ms Sobolewski).

Presented in part at the Ambulatory Pediatrics Association Annual Meeting, April 30, 1984.

Reprint requests to Division of Behavioral and Developmental Pediatrics, University of California, 400 Parnassus Ave, A203, San Francisco, CA 94143 (Dr Boyce).

school at which the injury occurred. Apparent causes of injury were coded as follows: (1) self-caused; (2) intentionally caused by another student; (3) accidentally caused by another student; (4) related to use of playground or sports equipment; (5) related to use of mechanical equipment; (6) athletics related; or (7) other.

For the purposes of the present study, *recurrent injuries* were defined as all school injuries sustained by a child during an academic year in which two or more injuries were reported for that child. Conversely, *single injuries* were defined as those occurring in a year in which only one injury was reported. Injuries were thus categorized as recurrent or single based on their occurrence in isolation or within a temporal cluster of similar events. Finally, *recurrently injured children* were defined as those children sustaining recurrent injuries in at least one of the three study years.

At the midpoint of the study period, in June 1982, principals and nurses completed questionnaires on school characteristics judged potentially important to the rate of injury within individual schools. These characteristics included five categories of ecological variables: demographic factors (student enrollment, percentage of minority students, and student-staff ratio), social factors (transience rate, absence rate, drug or alcohol problems, family stability in student population, and behavior problems), programmatic factors (elementary vs junior high vs high school, alternative educational programs, level of Parent-Teacher Association activity, and school hours), physical factors (age of school building and playground condition), and health program factors (variety and years of nursing experience, nursing education, nurse hours, presence of a nurse's aide, and presence of a safety program).

Alternative education programs ascertained included the presence of magnet curricula, open classrooms, and other educational features designed to promote voluntary desegregation. All principal and nurse questionnaires were completed without knowledge of the single or recurrent injury rates within the school.

Finally, the possibility of underreporting of injuries by individual schools was addressed using a telephone survey of parents at the end of the first school year. A random sample of 120 children with no school-reported injuries was selected from schools at the two ends of the injury rate distribution (ie, schools with low injury rates and schools with high injury rates). Children from schools with low injury rates were matched according to age and sex with the children from schools with high injury rates. Blind telephone interviews were then conducted with a parent of each child to ascertain parental recall of school-based injury events during the preceding academic year. This procedure thus provided an estimate of underreporting rates by schools at the low and high ends of the injury range.

Table 1.—Actual vs Predicted Distribution of Injuries Among 54 874 School children*

No. of Injuries per Child	Actual		Predicted	
	No. of Children	No. of Injuries	No. of Children	No. of Injuries
0	47 277	0	47 076	0
1	7024	7024	7216	7216
2	390†	780	554	1108
3	128†	384	27	81
4	41	164	1	4
5	9	45	0	0
6	4	24	0	0
≥7	1	8	0	0
Total	**54 874**	**8429**	**54 874**	**8409**
Subgroup with ≥2 injuries	573	1405	582	1193

*As predicted by the binomial distribution; χ^2 for difference in proportions = 149.4 with 7 *df*, $P<.001$.

†These values represent the number of recurrently injured children with two and three injuries during the three-year period; the true figures for the whole population are probably slightly higher because of children with two or three injuries occurring at a rate of one per year in separate years.

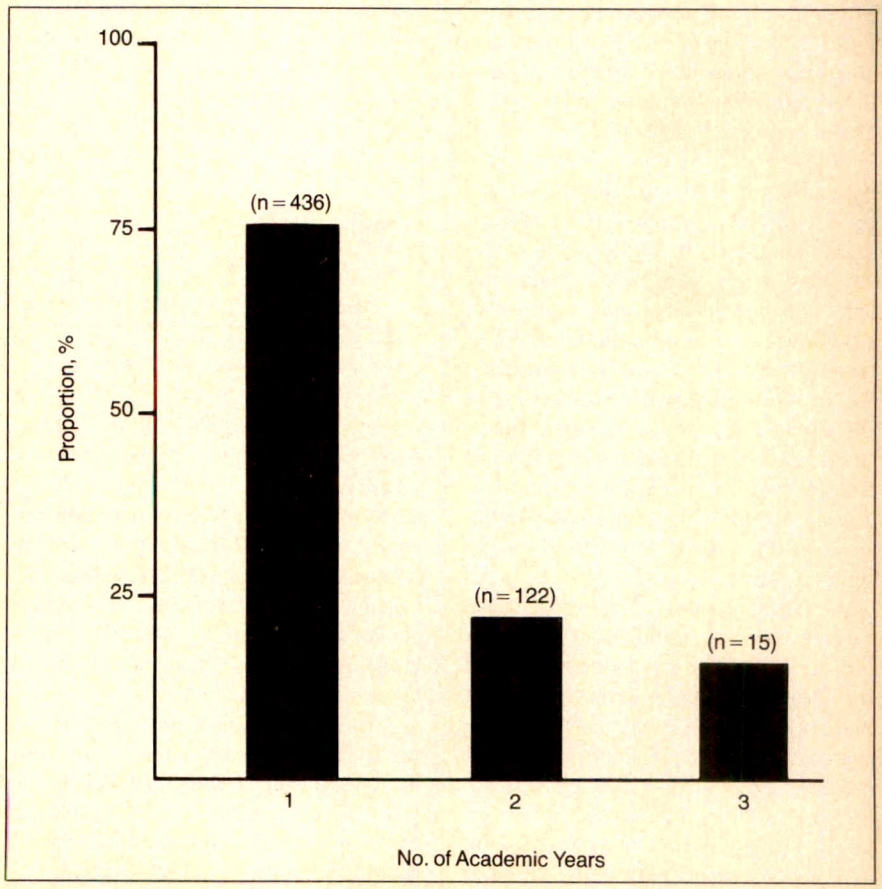


Fig 1.—Number of years injured among recurrently injured children (N = 573).

Statistical methods employed χ^2 tests for assessing differences in proportions, and analysis of variance was used to compare mean injury rates among two or more categories of schools.

RESULTS

A total of 8429 injuries were reported during the study period, with an approximately equal injury incidence found in each of the three study years. Table 1 shows a breakdown of the injury distribution in the entire student population and compares the observed distribution with that predicted by chance according to the binomial distribution. Although the observed distribution closely approximates the predicted distribution, a significantly greater proportion of students sustained two or more injuries than could be accounted for through the operation of chance. By chance alone, 582 students (1%) were expected to sustain two or more injuries, for a total of 1193 injury events (14% of the overall injury experience). By comparison, an actual subgroup of 573 children (1%) sustained two or more injuries totaling 1405 (17%) of the overall injury experience, a proportion close to but significantly greater than the predicted proportion ($P<.001$).

Within the recurrently injured subpopulation of students, the three-year total of injuries ranged from two to eight, as shown in Table 1, with the majority of children (68%) sustaining only two injuries. A small number of children (14, or approximately 2.5% of those recurrently injured) experienced five or more injuries over the course of the three study years. Figure 1 shows that most of the 573 recurrently injured children were injured during only one academic year, while a small subpopulation of 15 children (2.6% of those recurrently injured) received injuries in all three study years. Taken together, these observations indicate the following: (1) a small group of children (1% of the entire student population) sustained more injuries than could be expected on the basis of chance alone, and (2) most recurrently injured children experienced excessive injury rates for a relatively limited period of time, usually lasting one year or less. A few children constituting a very small subset of the entire student population (0.027% or approximately three in 10 000) had an extraordinarily high rate of injury that continued over the entire study period.

This latter finding of persistent injuries in a small subpopulation of students is further elucidated in Fig 2, which traces the subsequent injury experience of the 223 children recurrently injured in year 1. Forty-nine children (22%) in this group were injured again in year 2, and 15 (7%) sustained an injury in the third year as well. There was thus a small subset of students in whom a cluster of early injuries was followed by later injury events, in some cases in all three study years.

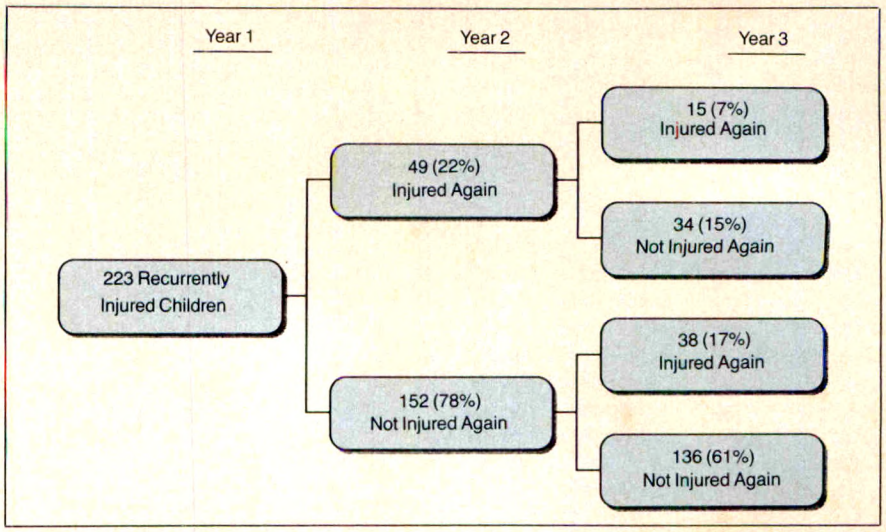


Fig 2.—Subsequent injury experience among recurrently injured children with injuries in year 1 (N = 223).

Table 2.—Injury Rates by Age and Sex

	Total No. of Students	No. (%) of Students Recurrently Injured
Age, y		
6-11	27 972	155 (0.6)
12-13	8619	147 (2.7)*
14-18	18 283	271 (1.5)
Sex		
M	27 437†	422 (1.5)*
F	27 437	151 (0.6)
Total	**54 874**	**573** (1.0)

*For difference in proportions, $\chi^2 = 136$ with 2 *df* for age, and $\chi^2 = 127$ with 1 *df* for sex ($P<.0001$).
†Assuming equal distribution of sexes.

As shown in Table 2, both age and sex were found to be correlates of recurrent injury experience. Only 0.6% of 6- to 11-year-old (elementary school) children were recurrently injured, whereas recurrently injured students constituted 2.7% and 1.5% of the junior high and high school age groups, respectively ($P<.001$). Similarly, a significantly greater proportion of boys was recurrently injured, with boys outnumbering girls almost 3:1 ($P<.001$).

Several differences were also found in the characteristics of the injuries among recurrent vs single occurrences. Table 3 displays the proportions of recurrent and single events with each of several injury characteristics. For example, recurrent injuries were 1.5 times more likely to have been sustained during athletic activities, a significant increase over the proportion of single injuries that were sports related. Recurrent injuries were also significantly more likely to have occurred outside of regular school hours (but on school grounds, by definition) and were less likely to have been severe.

Finally, and similar to our previous reports[9,34] on school-related injuries, rates of recurrent injuries were highly variable among schools. School-specific rates of recurrent injury ranged from zero in 25 schools up to greater than 25 per 1000 student-years in a few schools. One plausible explanation for the observed variability in recurrent injury was the possibility that underreporting

Table 3.—Injury Characteristics Among Recurrent vs Single Injuries

Injury Characteristic	Proportion With Indicated Characteristics, %		Relative Likelihood Among Recurrent Injuries*
	Recurrent Injuries	Single Injuries	
Athletics-related	29†	20	1.5
Occurred on playground or in gym	63	65	1.0
Occurred outside school hours	21†	15	1.4
Severe (eg, amputation fracture, concussion)	13†	18	0.7

*Relative likelihood indicates the proportion of recurrent injuries with the indicated characteristic divided by the proportion of single injuries with the indicated characteristic.
†$P<.0001$ by χ^2 for difference between proportion, with 1 *df*.

Table 4.—Ecologic Associations With School-Specific Rates of Recurrent Injury

Programmatic Characteristic	Mean School-Specific Injury Rate
School hours*	
Regular	3.2
Extended	13.7
Alternative educational programs†	
Absent	2.9
Present	8.2
Category of School‡	
Elementary	4.0
Junior high school	18.2
High school	10.7

*$F=12.9$ ($P<.001$).
†$F=10.3$ ($P<.002$).
‡$F=3.8$ ($P<.01$).

occurred in the schools with low injury rates. However, the rates of underreporting were estimated using the telephone parent interview described above and were found to be virtually identical in schools with low injury rates and schools with high injury rates (11% and 12%, respectively). Thus, differences in underreporting were not a likely explanation of differences in recurrent injury rates.

Table 4 identifies the ecologic variables that significantly covaried with school-specific rates of recurrent injury. Because of the number of variables examined, only those associated with recurrent injury rates at $P\leq.01$ are shown as significant. Extended school hours and the presence of alternative educational programs (such as "open" classrooms and magnet curricula) were both significantly associated with higher rates of recurrent injury. As previously suggested by the analysis of recurrent injuries by age, junior high schools also had significantly higher rates.

COMMENT

The results of the present study indicate that approximately one in 100 children were recurrently injured in school settings when followed up prospectively over a three–academic year period. Although the proportion of children recurrently injured was small, this subgroup sustained nearly one fifth of all injuries reported, a proportion modestly but significantly greater than that expected on the basis of chance alone. The study thus documents a disproportionate injury experience among a particular subpopulation of school-age children.

Among recurrently injured children, most sustained only two injuries, and the vast majority of injuries were clustered within a short time. A very small group of children experienced injuries in every year, sustaining as many as eight over the course of the entire study period. Results of the present study therefore suggest that recurrent injuries occur most often in episodic clusters and that recurrently injured schoolchildren generally manifest only transient periods of heightened risk.

Demographic and ecologic correlates of recurrent injury experience indicated that injuries were most likely to recur in junior high school boys, among those children engaged in athletic activities, and in children attending schools with extended hours and alternative educational programs. Certain of these findings, such as the overrepresentation of boys and sports-related events, are in agreement with findings in other studies that have addressed injury epidemiology in childhood populations.[9-11] Furthermore, the peak rate of recurrent injuries during the junior high school years is similar to data from the previous reports by Sheps and Evans[10] and Feldman et al.[11] In both studies, the highest annual rates of injury were found among children in the junior high school years. Finally, our ecologic results for recurrent injuries parallel those previously reported[9] for school-related injuries in general. For both single and recurrent injuries, there appears to be a disproportionately high rate of occurrence in schools with alternative curricula and prolonged school hours.

How do these results inform the ongoing debate on the existence and character of the injury-prone child? In their 1964 review, Froggatt and Smiley[18] proposed a modification of the injury proneness concept based on evidence accumulated to that date. The core of their proposed modification was as follows: (1) injury proneness is not a stable entity but changes for each person over time, and (2) individuals persistently prone to injury constitute only a very small proportion of any given population. The results of the present study confirm, within a childhood population, the proposals advanced by Froggatt and Smiley.[18] Our data suggest that when a population of children is studied over a period of years, a small subgroup that represents only 1% of the original population will sustain a period of recurrent injury. However, as stated by Reason,[35] "Examination of accident-repeaters over a lengthy period indicates that they are members of a club which is constantly changing its membership. New people are added, while longstanding members cease to qualify." The vast majority of recurrently injured children appear to enter, and subsequently leave, a period of temporary vulnerability in which an unusual clustering of injuries occurs. Only an extraordinarily small group of children—perhaps as few as three in 10 000—seem to maintain an inordinate risk of injury over an extended period of years.

It is plausible to argue that the periods of enhanced injury vulnerability noted in the present study may have resulted from the combined or interactive effects of developmental and social environmental factors. A developmen-

tal vulnerability is suggested by the significantly increased recurrent injury rates found during the junior high school years, a transition period with both biologic and psychologic risks noted previously by Schor.[12] The importance of the social environment, on the other hand, is suggested by the finding that programmatic characteristics of the schools were significant correlates of school-specific recurrent injury rates. Furthermore, past work from a variety of sources[31,36-39] indicates the potential influence of family environmental factors (such as family stressors, family disorganization, and parental depression) on health and illness in childhood populations. It is thus conceivable that a child's transient pattern of injury recurrence could result from the occurrence of school or family stressors during a stage of particular developmental vulnerability.

Results of the present study have several implications for future research on the prevention of childhood injuries. First, the present results suggest the need for well-designed case-control studies of recurrently injured children. By closely examining the psychosocial experiences and behavioral characteristics of recurrently injured children, new information regarding the determinants of recurrent injuries may be forthcoming. Preventive strategies targeting recurrently injured children will be particularly useful and effective because of the disproportionate share of the overall injury experience sustained by these children. In addition, since most recurrent injuries seem to occur in relatively short-lived episodes, interventions could potentially focus on specific periods of enhanced vulnerability if the characteristics of those periods could be identified.

Second, the study offers additional rationale for the development of environmental, school-based approaches to injury prevention. Since the school setting appears to be an important correlate of recurrent injury rates, environmental strategies designed to reduce school-related causative factors may have important advantages over individual approaches to altering risk.[40]

Finally, the present study indicates the need for more extensive investigation of psychosocial and developmental influences on injuries and injury-associated behaviors. The elucidation of critical developmental periods in injury occurrence, for example, would have important implications for preventing injuries and would allow intervention programs to focus on specific categories of developmentally at-risk children. Further study of family stressors as predictors of recurrent injury may also provide insights for the design of new preventive strategies. By providing an epidemiologic view of recurrent injuries among school-age children, this study, it is hoped, will advance the growing interest in injury as a source of childhood morbidity and suggest new approaches to the prevention of injuries in schools.

We gratefully acknowledge the editorial contributions of Marilyn Winkleby, PhD, and David Ragland, PhD, to earlier drafts of this work. We are also indebted to the school nurses and principals who provided the data on which this report is based.

References

1. World Health Organization: Health of the world's children. *WHO Chron* 1979;33:119-127.
2. Baker SP, O'Neill B, Karg R: *The Injury Fact Book*. Lexington, Ky, DC Heath & Co, 1984.
3. Guyer B, Gallagher S: An approach to the epidemiology of childhood injuries. *Pediatr Clin North Am* 1985;32:5-15.
4. *Vital and Health Statistics: Current Estimates from the National Health Interview Survey*, Department of Health and Human Services publication 82-1567, Hyattsville, Md, National Center for Health Statistics, 1981.
5. Rivara FP, Bergman AB, LoGerfo JP, et al: Epidemiology of childhood injuries: Sex differences in injury rates. *AJDC* 1982;136:502-506.
6. Rivara FP: Epidemiology of childhood injuries: I. Review of current research and presentation of conceptual framework. *AJDC* 1982;136: 399-405.
7. Baker SP: Determinants of injury and opportunities for intervention. *Am J Epidemiol* 1975;101:98-102.
8. Pless IB, Stulginskas J: Accidents and violence as a cause of morbidity and mortality in childhood. *Adv Pediatr* 1982;29:471-495.
9. Boyce WT, Sprunger LW, Sobolewski S, et al: Epidemiology of injuries in a large, urban school district. *Pediatrics* 1984;74:342-349.
10. Sheps SB, Evans GD: Epidemiology of school injuries: A two-year experience in a municipal health department. *Pediatrics* 1987;79:69-75.
11. Feldman W, Woodward CA, Hodgson C, et al: Prospective study of school injuries: Incidence, types, related factors and initial management. *Can Med Assoc J* 1983;129:1279-1283.
12. Schor EL: Use of health care services by children and diagnoses received during presumably stressful life transitions. *Pediatrics* 1986;77: 834-841.
13. Schinke SP, Schilling FR, Snow WH: Stress management with adolescents at the junior high transition: An outcome evaluation of coping skills intervention. *J Human Stress* 1987;13:16-22.
14. Chang A, Lugg MM, Nedebum A: Injuries in preschool children enrolled in day care centers. *Pediatrics*. In press.
15. Bijur PE, Stewart-Brown S, Butler N: Child behavior and accidental injury in 11 966 preschool children. *AJDC* 1986;140:487-492.
16. Gallagher SS, Finison K, Guyer B, et al: The incidence of injuries among 87 000 Massachusetts children and adolescents: Results of the 1980-81 Statewide Childhood Injury Prevention Program Surveillance System. *Am J Public Health* 1984;74:1340-1347.
17. Manheimer DI, Mellinger GD: Personality characteristics of the child accident repeater. *Child Dev* 1967;38:491-513.
18. Froggatt P, Smiley JA: The concept of accident proneness: A review. *Br J Indust Med* 1964;21:1-12.
19. Connolly J: Accident proneness. *Br J Hosp Med* 1981;26:470-479.
20. Sass R, Crook G: Accident proneness: Science or non-science? *Int J Health Serv* 1981;11: 175-190.
21. Farmer E, Chambers EG: A psychological study of individual differences in accident rates. London, Industrial Fatigue Research Board, report No. 38, 1926.
22. Langley J, Silva PA, Williams S: A study of the relationship of 90 background developmental behavioural and medical factors to childhood accidents: A report from the Dunedin Multidisciplinary Child Development Study. *Aust Paediatr J* 1980;16:244-247.
23. Langley J: The 'accident prone' child: The perpetration of a myth. *Aust Paediatr J* 1982; 18:243-246.
24. Langley J, McGee R, Silva P, et al: Child behavior and accidents. *J Pediatr Psychol* 1983;8:181-189.
25. Langley J, Dodge J, Silva PA: Accidents in the first five years of life: A report from the Dunedin Multidisciplinary Child Development Study. *Aust Paediatr J* 1979;15:255-259.
26. Husband P: The accident-prone child. *Practitioner* 1973;211:335-344.
27. Eminson CJ, Jones H, Goldacre M: Repetition of accidents in young children. *J Epidemiol Community Health* 1986;40:170-173.
28. Jones JG: The child accident repeater. *Clin Pediatr* 1980;19:284-288.
29. Mellinger GD, Manheimer DI: An exposure-coping model of accident liability among children. *J Health Soc Behavior* 1967;8:96-106.
30. Matheny AP: Visual-perceptual exploration and accident liability in children. *J Pediatric Psychol* 1980;5:343-351.
31. Husband P, Hinton PE: Families of children with repeated accidents. *Arch Dis Child* 1972; 47:396-400.
32. Sims ACP: Head injury, neurosis and accident proneness. *Adv Psychosom Med* 1985;13: 49-70.
33. McCormick MC, Shapiro S, Starfield BH: Injury and its correlates among 1-year-old children. *AJDC* 1981;135:159-163.
34. Boyce WT, Sobolewski S, Sprunger LW, et al: Playground equipment injuries in a large, urban school district. *Am J Public Health* 1984;74: 984-986.
35. Reason J: Style, personality and accidents. *New Society* 1974;27:445-448.
36. Meyer RJ, Roelofs HA, Bluestone J, et al: Accidental injury to the preschool child. *J Pediatrics* 1963;63:95-105.
37. Schor EL: Unintentional injuries: Patterns within families. *AJDC* 1987;141:1280-1284.
38. Horwitz SM, Morgenstern H, DiPietro L, et al: Determinants of pediatric injuries. *AJDC* 1988;142:605-611.
39. Padilla ER, Rohsenow DJ, Bergman AB: Predicting accident frequency in children. *Pediatrics* 1976;58:223-226.
40. Wallack L, Winkleby M: Primary prevention: A new look at basic concepts. *Soc Sci Med* 1987;25:923-930.

Prostaglandin E_1 Selectively Reduces Group B β-Hemolytic Streptococci–Induced Pulmonary Hypertension in Newborn Piglets

Cathy Hammerman, MD; Mary Jane Aramburo, MD; Jung-Hwan Choi, MD; Val Hill

• Group B β-hemolytic streptococci (GBS)–induced pulmonary hypertension was generated in ten newborn piglets. Intravenous infusions of either prostaglandin E_1 (PGE_1) (n = 5) or placebo (n = 5) were begun after 60 minutes of stable pulmonary hypertension. The effects of these interventions on cardiopulmonary hemodynamics were studied. Pulmonary artery pressure (PAP) increased similarly in both groups during the first 60 minutes of GBS infusion. By two hours after intervention, PAP was significantly lower in the animals given PGE_1 (20 ± 4 vs 32 ± 5 mm Hg for PGE_1 vs placebo). The ratio of pulmonary to systemic vascular resistance followed a pattern analogous to PAP, increasing with the GBS infusion, indicating selective pulmonary vasoconstriction. The pulmonary vascular resistance/systemic vascular resistance ratio decreased after intervention in the group given PGE_1 only (0.25 ± 0.08 vs 0.50 ± 0.12 for PGE_1 vs placebo), indicating selective pulmonary vasodilation. Transient systemic hypotension was noted at one hour after initiation of PGE_1 infusion. Prostaglandin E_1 infusion selectively improved GBS-induced pulmonary hypertension and hypoxemia in newborn piglets with only transient systemic hypotension.

(*AJDC* 1989;143:343-347)

Neonatal sepsis is often associated with a persistent elevation of pulmonary artery pressure (PAP). Under normal circumstances, the transition from intrauterine to extrauterine life is associated with a rapid reduction in pulmonary vascular resistance (PVR) from the suprasystemic levels characteristic of fetal life to the much lower levels associated with postnatal life. In the face of irritant stimuli, however, these changes may fail to occur and pulmonary hypertension ensues.

Most therapeutic research relating to this condition has focused on the search for a selective pulmonary vasodilator that might be able to alleviate this pulmonary vasoconstriction without causing significant systemic hypotension. Our study focuses on a new alternative, yet an old drug—prostaglandin E_1 (PGE_1). This powerful vasodilator, although not selective for the pulmonary vascular bed, is almost completely metabolized on one pass through the pulmonary circulation. Thus, significant levels would not be expected to reach the systemic circulation, and thereby would not be expected to cause significant hypotension.

Our study was undertaken, therefore, to test the hypothesis that group B β-hemolytic streptococci (GBS)–induced pulmonary hypertension in a piglet model will respond to the infusion of the vasodilator PGE_1 with a selective and prolonged reduction in PAP.

MATERIALS AND METHODS

Surgical Preparation

Two- to 3-week-old Sus Scrofa piglets were sedated with ketamine (20 mg/kg intramuscularly), anesthetized with intravenous pentobarbital sodium (20 mg/kg initially; 2 mg/kg/h subsequently), and endotracheally intubated. Muscle relaxation was achieved with tubocurarine (1 mg/kg). A mechanical ventilator (Harvard Medical Supplies, Dover, Mass) was adjusted to maintain arterial partial pressure of carbon dioxide ($Paco_2$) at about 35 mm Hg (volumes ranged from 100 to 150 mL; respiratory rates ranged from 12 to 16 /min) initially. All piglets were ventilated with a fraction of inspired oxygen of 0.60 to prevent any hypoxic component of the GBS infusion from independently affecting PAP.[1] No changes were made in ventilatory values once stabilization was achieved and the experimental phase of the protocol was begun. Warming blankets and overhead heating lamps were used to maintain body core temperature at 38°C to 39°C. A suprapubic cystotomy catheter was placed to establish urinary drainage in the paralyzed animal.

Two polyethylene catheters providing venous access were placed surgically into the external jugular vein. Intravascular catheters attached to pressure transducers were placed in the aorta (via the carotid artery), the right atrium (via the external jugular vein) and the left atrium (via the appendage), and the pulmonary artery (via a left lateral thoracotomy). An external electromagnetic flow probe (Carolina Medical Electronics, King, NC) was placed around the pulmonary artery, visualized via the left lateral thoracotomy, proximal to the tip of the pulmonary artery catheter. During each experiment, the pulmonary artery flow probe was zeroed frequently using the approximation that diastolic blood flow in the pulmonary artery is zero.

Mean pressures were obtained by electrical integration. The following hemodynamic variables were measured directly and continuously: phasic and mean aortic pressure (AOP), phasic and mean PAPs, phasic and mean central venous pressure (CVP), phasic and mean left atrial pressure (LAP), pulmonary artery blood flow, and heart rate. In the assumed absence of right-to-left and left-to-right shunts, pulmonary artery blood flow was accepted as the equivalent of cardiac output (CO). From these monitored hemodynamic values, systemic vascular resistance (SVR) was calculated as (AOP – CVP)/CO, and PVR was calculated as (PAP – LAP)/CO.

Experimental Protocol

Control hemodynamic measurements were taken and determined to be stable for at least one hour after the surgery in all animals. Hemodynamic variables were monitored continuously in all animals. Group B β-hemolytic streptococci infusions were begun

Accepted for publication Nov 14, 1988.

From the Department of Pediatrics, University of Chicago Medical Center. Dr Choi is now with the Seoul (Korea) National University Children's Hospital.

Reprint requests to Department of Pediatrics, Box 325, University of Chicago Medical Center, Chicago, IL 60637 (Dr Hammerman).

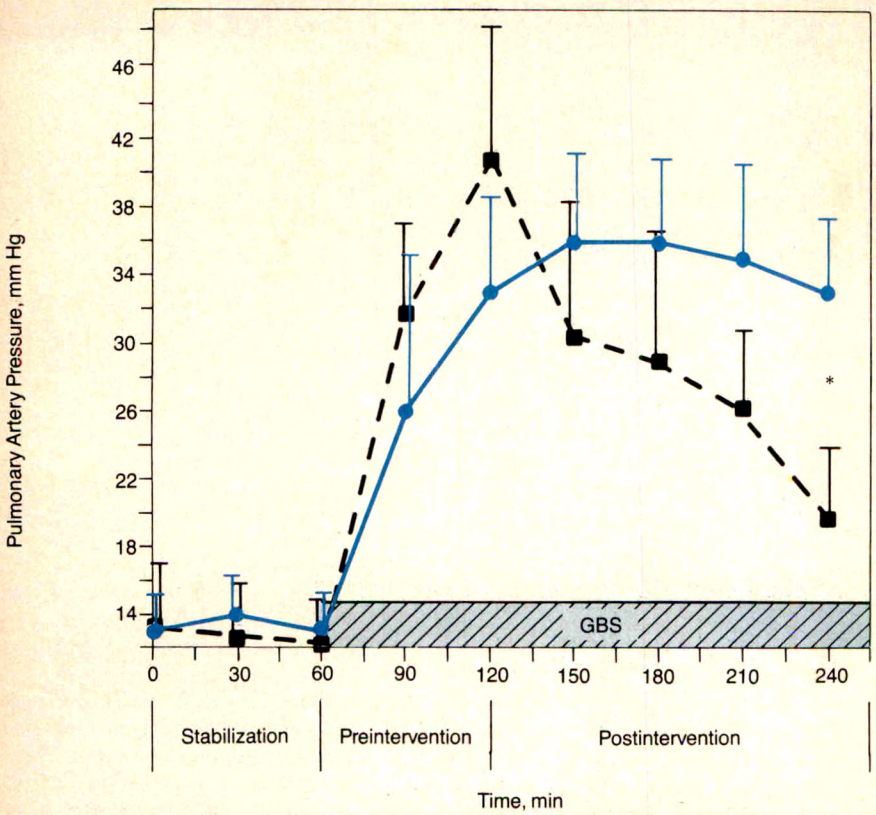


Fig 1.—Pulmonary artery pressure in piglets receiving prostaglandin E_1 (PGE_1) vs piglets receiving placebo (mean ± SD). Pulmonary artery pressure values are plotted serially in relation to time for piglets receiving group B β-hemolytic streptococci (GBS) and PGE_1 and piglets receiving GBS and placebo. Stabilization, pulmonary hypertension, preintervention, and postintervention phases are delineated. Pulmonary artery pressures of piglets receiving PGE_1 are lower than those of piglets receiving placebo at 240 minutes. Circles indicate piglets receiving placebo; squares, piglets receiving PGE_1; and asterisk, $P<.05$.

after 60 minutes and continued for three hours. After the initial hour, and as the GBS infusion continued, the animals were divided into two groups: one to receive an infusion of PGE_1 and the other to receive placebo (vehicle). For purposes of clarification and comparison, experimental data are divided into three segments:

1. *Preintervention stabilization:* the period extending from the completion of the surgical procedure until one hour after stabilization of monitored vital signs and hemodynamics. Baseline measurements are defined as those occurring at the end of this interval.

2. *Group B β-hemolytic streptococci preintervention:* the period beginning with the GBS infusion, lasting 60 minutes, and characterized by the establishment of stable pulmonary hypertension (defined as an increase in PAP to 150% to 200% of baseline, sustained at this level ± 10% for 60 minutes).

3. *Group B β-hemolytic streptococci postintervention:* the second and third hours of continued GBS infusion, beginning with administration of either the PGE_1 or the placebo.

The hemodynamic values compared were preselected to be those from the end of each segment to demonstrate maximal change. It should be noted that segments 1 and 2 are each one hour long, while the third segment lasts two hours.

Arterial blood samples (from the carotid artery catheter) were drawn at the end of each experimental segment for the measurement of blood gases (IL 713, Instrumentation Laboratories, Lexington, Mass).

Preparation of Bacteria

Group B β-hemolytic serotype 1b streptococci previously isolated from an infected human newborn were grown in 250 mL of Todd-Hewitt broth to late log phase (equivalent 1×10^9 organisms/mL). The bacteria were centrifuged, the supernatant was decanted, and the organisms were resuspended to their original concentration in 5% dextrose in water/lactated Ringer's solution. The GBS infusion rate was increased slowly in a stepwise manner from 0.5×10^7 organisms/kg/min to 0.5×10^8 organisms/kg/min.

The PGE_1 (Prostin) was diluted in alcohol to make a stock solution that was then frozen at −60°C. At the time of each experiment, one vial of the above was thawed and further diluted in isotonic saline solution. Prostaglandin E_1 was infused through one of the venous catheters whose tip was advanced into the right atrium. Infusions were begun at 0.1 μg/kg/min and increased by 0.1-μg/kg/min increments every half hour if PAP was greater than or equal to 25 mm Hg.

STATISTICAL ANALYSIS

Means ± SDs were computed for all measured variables in both groups. Intergroup differences for a given variable were compared using a Student t test for unpaired samples. Intragroup differences were calculated for each variable for the time extending from the end of one period to the end of the next and then compared using repeated measured analyses of variance. Where a significant difference was noted, pairwise comparisons were made by a two-tailed paired t test with Bonferroni correction to compensate for repeated measures.

RESULTS

Ten piglets underwent surgical preparation and line placement as described above. Five received GBS and PGE_1 and five were given GBS and placebo. The mean weight at the time of study for the animals receiving PGE_1 was 3.97 ± 0.44 kg compared with 3.88 ± 0.37 kg for the animals receiving the placebo. There were no differences with respect to the amounts or types of fluid administered, hematocrit values, or baseline hemodynamic variables.

Intergroup and Intragroup Hemodynamics

As Fig 1 demonstrates, all piglets developed significant pulmonary hypertension with GBS infusion. Mean PAPs rose from 13 ± 4 and 13 ± 5 to 40 ± 14 and 33 ± 4 mm Hg in the groups receiving PGE_1 and placebo, respectively, by 120 minutes (60 minutes of GBS infusion) ($P<.05$ compared with baseline for both). During this time the PVR/SVR ratio (Table) also increased significantly while SVR remained unchanged, indicating the generation of selective pulmonary vasoconstriction in both groups.

After intervention, PAP declined only in the animals receiving PGE_1. Furthermore, it continued to drop throughout the ensuing two hours, thereby eliminating the second phase

characteristically seen in treated GBS-induced pulmonary hypertension in this model (20 ± 4 vs 33 ± 5 mm Hg for the groups receiving PGE_1 and those receiving placebo, respectively, at 240 minutes; $P<.05$). The PVR/SVR ratio decreased concurrently in the group receiving PGE_1.

Aortic pressure (Fig 2) dropped in both groups with the progression of sepsis. It was lower in animals receiving PGE_1 compared with those receiving placebo at 180 minutes ($P<.05$). However, AOP improved with time, and the differences ceased to be significant at 210 and 240 minutes.

There were no significant changes in CVP or LAP with time. As the Table demonstrates, heart rate and CO were similar throughout the study between the groups, although heart rate increased with the continued GBS infusions and cardiac index decreased compared with baseline values. The PVR/SVR ratio was different, as described above.

Blood Gases

As is demonstrated in the Table, arterial partial pressure (Pa_{O_2}) dropped in both groups of animals compared with baseline; however, this decrease was somewhat protected by the PGE_1 infusions (final Pa_{O_2} was 140 ± 31 mm Hg for piglets receiving PGE_1 vs 96 ± 37 mm Hg for piglets receiving placebo; $P<.05$). Arterial partial pressure of carbon dioxide and pH were not significantly different between groups.

COMMENT

Neonatal pulmonary vessels exhibit hyperreactive vasoconstrictive responses[2] to irritant stimuli that, although adaptive in utero, postnatally serve to accentuate the precipitating insult. Such responses render newborns extremely susceptible to pulmonary hypertension. Furthermore, once pulmonary vasoconstriction has been induced, it often persists even after removal of the initial stimulus, suggesting the presence of some biochemical mediator.

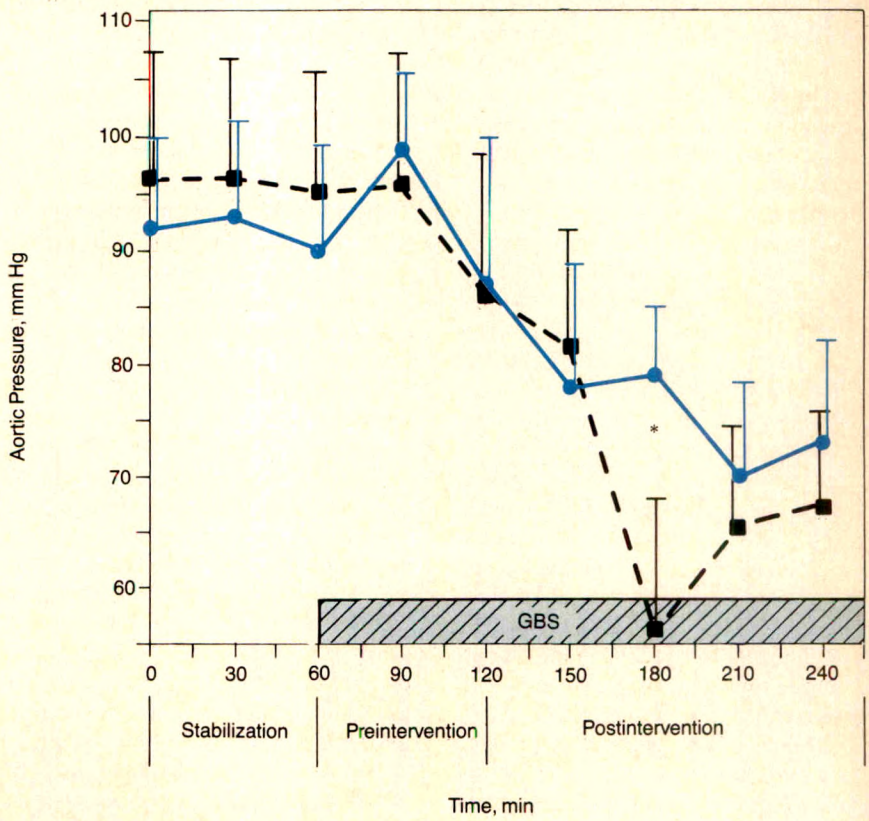
The search to identify this mediator(s) has been extensive. Prostanoids are potent vasoactive substances that have been implicated in the development of pulmonary hypertension. Abnormally high levels of the prostanoid

Hemodynamic Variables*						
	Stabilization		GBS Preintervention		Postintervention	
	PGE_1	Placebo	PGE_1	Placebo	PGE_1	Placebo
Heart rate, beats per minute	152 ± 51	183 ± 48	161 ± 26	187 ± 44	214 ± 35†	198 ± 40†
Cardiac index, mL/min/kg	120 ± 35	122 ± 26	89 ± 31†	93 ± 24†	86 ± 7†	91 ± 22†
PVR/SVR	0.10 ± .10	0.12 ± .05	0.47 ± .19†	0.38 ± .16†	0.25 ± .08†	0.50 ± .12†
Pa_{O_2}	216 ± 53	239 ± 45	199 ± 72	188 ± 46	140 ± 31†	96 ± 37†
Pa_{CO_2}	32 ± 3	31 ± 2	34 ± 5	33 ± 3	34 ± 8	40 ± 5
pH	7.45 ± .04	7.43 ± .05	7.41 ± .04	7.36 ± .03	7.32 ± .07†	7.28 ± .05†

*All data are expressed as the mean ± SD. GBS indicates group B streptococci; PGE_1, prostaglandin E_1; PVR/SVR, pulmonary vascular resistance/systemic vascular resistance; Pa_{O_2}, arterial partial pressure of oxygen; and Pa_{CO_2}, arterial partial pressure of carbon dioxide. All intergroup differences were not significant, except for the postintervention phase of PVR/SVR and Pa_{O_2} ($P<.05$).

†$P<.05$, compared with baseline level for same variable within group.

Fig 2.—Aortic pressure in piglets receiving prostaglandin E_1 (PGE_1) vs piglets receiving placebo (mean ± SD). Aortic pressure is plotted serially in relation to time for piglets receiving group B β-hemolytic streptococci (GBS) and PGE_1 and piglets receiving GBS and placebo. Stabilization, pulmonary hypertension, preintervention, and postintervention phases are delineated. Aortic pressures of piglets receiving PGE_1 are lower than those of piglets receiving placebo at 180 minutes. Circles indicate piglets receiving placebo; squares, piglets receiving PGE_1; and asterisk, $P<.05$.



vasoconstrictor thromboxane are associated with the development of GBS-induced pulmonary hypertension[3,4] in several animal models. High levels of thromboxanes have also been demonstrated in human neonates with persistent pulmonary hypertension of the newborn.[5] Furthermore, both prophylactic and therapeutic use of either cyclooxygenase inhibitors[3,4] or thromboxane synthetase-specific inhibitors[1,6] are able to prevent or ameliorate the thromboxane rise, the pulmonary vasoconstriction and the hypoxemia of GBS sepsis in the newborn animal model.

Other studies have focused on the search for pulmonary-specific vasodilators. Prostaglandin D_2 has been described to selectively decrease PAP in fetal animals[7,8] with hypoxic pulmonary vasoconstriction. However, preliminary data suggest little clinical efficacy for PGD_2 in human neonates with persistent pulmonary hypertension of the newborn.[9] Prostacyclin (PGI_2) is the major prostanoid released during ventilation of perfused lungs,[10] and PGI_2 infusions have been noted to cause pulmonary vasodilation in hypoxic piglets.[11] Preliminary studies of the clinical use of PGI_2 infusions in human neonates with persistent pulmonary hypertension of the newborn have been promising.[12,13] However, therapeutic administration of PGI_2 was abandoned after a brief and unsuccessful multicentered clinical trial in which most of the infants' conditions deteriorated and only two of 13 survived.[14]

Prostaglandin E_1 is a prostaglandin vasodilator that causes both pulmonary and systemic vasodilation.[15,16] Even though PGE_1 does not have a selective pulmonary effect, because it is largely (≥95%) metabolized in one pass through the lungs,[17] PGE_1 has been hypothesized to be able to exert greater pulmonary than systemic effects if infused intravenously. The animals in our study treated with PGE_1 did show a transient systemic hypotension at 180 minutes, compared with the placebo-treated animals. One can only speculate as to the mechanism for this. It is possible that there is some lag time until the pulmonary catabolic enzymes become activated.

In animals with GBS-induced pulmonary hypertension treated with thromboxane-specific and/or cyclooxygenase inhibitors, a secondary rise in PAP develops about one hour after administration of the inhibitor.[4,18-20] This phase is felt by many to be caused by a leukotriene-mediated increase in pulmonary vascular permeability,[21] leading to pulmonary edema. Because it is not thromboxane mediated, this secondary phase of pulmonary hypertension does not respond to either thromboxane or general cyclooxygenase inhibition. However, this later rise in PAP was not observed in the animals that received PGE_1 infusions. This observation is interesting in light of previous data that demonstrate that PGE_1 prevents increased lung microvascular permeability during intravascular complement activation in sheep[22] and attenuates oxidant-induced pulmonary edema in rat lungs.[23]

The relevance of this animal model of GBS sepsis to pulmonary hypertension in the human neonate has been well recognized.[24] It is not, however, a specific model for the persistent pulmonary hypertension of the newborn syndrome because the ductus arteriosus in the piglet is closed. These differences do make the clinical extrapolation of such laboratory findings necessarily tenuous. Nevertheless, we feel that this preparation affords us an opportunity to study the selective hemodynamic effects of pharmacologic manipulations on the pulmonary vasculature in a reproducible fashion. Furthermore, because of the similarities to human pulmonary hypertension and because of the persistently high morbidity and mortality associated with persistent pulmonary hypertension of the newborn, we feel that the potential clinical application of these studies does deserve some consideration.

If one were to contemplate potential therapeutic applications, the approach suggested by our study offers the following several advantages compared with the earlier studies described: (1) The use of a general cyclooxygenase inhibitor, such as indomethacin, in the human neonate with persistent pulmonary hypertension is contraindicated because of hypothetical complications attendant to ductal constriction, eliminating an important diversionary pathway for right ventricular outflow in the face of severe pulmonary hypertension. (2) Fetal administration of cyclooxygenase inhibitors is reported to contribute to an increased incidence of persistent pulmonary hypertension of the newborn.[25-27] This increases hesitation concerning the administration of such a substance to the neonate with persistent pulmonary hypertension of the newborn. (3) Thromboxane-specific inhibitors/antagonists, although they offer an exciting alternative, are not currently available for use in the human neonate. (4) The use of PGE_1 offers the advantage of extensive neonatal experience. It is frequently used to maintain ductal patency in infants with cyanotic congenital heart disease. In this context, significant hypotension is not observed. (5) Prostaglandin E_1 has been reported to relieve human pulmonary hypertension in the adult[28-31] and in one 11-year-old child with primary pulmonary hypertension.[32]

In summary, our study provides the following new observations: that PGE_1 administration ameliorates the acute hemodynamic effects of GBS infusion on the pulmonary vasculature; that PGE_1 administration ameliorates the drop in PaO_2 that results from GBS infusion; that the pulmonary vasodilation that occurs is associated with only a transient systemic hypotension when the PGE_1 is infused intravenously; and that the secondary phase of GBS-induced pulmonary hypertension, commonly seen when the PAP is reduced via the administration of thromboxane and/or cyclooxygenase inhibitors, is eliminated with the continuous infusion of PGE_1, or at least delayed for up to three hours after the initiation of GBS infusion.

The authors thank Soledad Callejas of Upjohn Pharmaceuticals, Kalamazoo, Mich, for her gracious donation of PGE_1.

References

1. Truog W, Sorensen G, Standaert T, et al: Effects of the thromboxane synthetase inhibitor dazmegrel (UK 38,485) on pulmonary gas exchange and hemodynamics in neonatal sepsis. *Pediatr Res* 1986;20:481-486.

2. Reid L: Structure and function in pulmonary hypertension: New perceptions. *Chest* 1986;89:279-288.

3. Rojas J, Larsson L, Ogletree M, et al: Effects of cyclooxygenase inhibition on the response to group B streptococcal toxin in sheep. *Pediatr Res* 1983;17:107-110.

4. Runkle B, Goldberg R, Streitfeld M, et al: Cardiovascular changes in group B streptococcal sepsis in the piglet: Response to indomethacin and relationship to prostacyclin and thromboxane A_2. *Pediatr Res* 1984;18:874-878.

5. Hammerman C, Lass N, Strates E, et al:

Prostanoids in neonates with persistent pulmonary hypertension. *J Pediatr* 1987;110:470-472.

6. Hammerman C, Komar K, Meadow W, et al: Selective inhibition of thromboxane synthetase reduces group B β hemolytic streptococci induced pulmonary hypertension in piglets. *Dev Pharmacol Ther* 1988;11:306-312.

7. Soifer S, Morin F, Heymann M: Prostaglandin D_2 reverses induced pulmonary hypertension in newborn lambs. *J Pediatr* 1982;100:458-462.

8. Cassin S, Tod M, Philips J, et al: Effects of prostaglandin D_2 on perinatal circulation. *Am J Physiol* 1981;240:H755-H760.

9. Soifer S, Clyman, Heymann M: Effects of prostaglandin D_2 on pulmonary arterial pressure and oxygenation in newborn infants with persistent pulmonary hypertension. *J Pediatr* 1988;112:774-777.

10. Leffler C, Hessler J: Perinatal pulmonary prostaglandin production. *Am J Physiol* 1981; 241:H756-H759.

11. Starling M, Neutze J, Elliott R: Control of elevated pulmonary vascular resistance in neonatal swine with prostacyclin (PGI_2). *Prostaglandins Med* 1979;3:105-117.

12. Lock J, Olley P, Coceani F: Direct pulmonary vascular responses to prostaglandins in the newborn lamb. *Am J Physiol* 1980;238:H631-H638.

13. Kaapa P, Koivisto M, Ylikorkala O, et al: Prostacyclin in the treatment of neonatal pulmonary hypertension. *J Pediatr* 1985;107:951-953.

14. Peckham G: Risk-benefit relationships of current therapeutic approaches, in Peckham G, Heyman MA (eds): *Cardiovascular Sequelae of Asphyxia in the Newborn*. Report of the Eighty-Third Ross Conference on Pediatric Research. Columbus, Ohio. Ross Laboratories, 1982, pp 110-116.

15. Tripp M, Drummond W, Heymann M, et al: Hemodynamic effects of pulmonary arterial infusion of vasodilators in newborn lambs. *Pediatr Res* 1980;14:1311-1315.

16. Philips J, Westfall M, Oliver J, et al: Effects of prostaglandins in two types of pulmonary hypertension, abstracted. *Pediatr Res* 1988;23:519A.

17. Robertson R: Differential in vivo pulmonary degradation of prostaglandin E_1, B_1 and A_1. *Am J Physiol* 1975;228:68-70.

18. Ahmed T, Wasserman M, Muccitelli R, et al: Endotoxin induced changes in pulmonary hemodynamic and respiratory mechanics: Role of lipoxygenase and cyclooxygenase products. *Am Rev Respir Dis* 1986;134:1149-1157.

19. Seeger W, Menger M, Walmrath D, et al: Arachidonic acid lipoxygenase pathways and increased vascular permeability in isolated rabbit lungs. *Am Rev Respir Dis* 1987;139:964-972.

20. Tafrey M, Graybar G, Lyrene R, et al: Thromboxane synthesis inhibition reverses group B streptococcus induced pulmonary hypertension. *Crit Care Med* 1987;15:644-647.

21. Kubo K, Kobayashi T: Effects of OKY-046, a selective thromboxane synthetase inhibitor on endotoxin induced lung injury in unanesthetized sheep. *Pediatr Res* 1981;15:899-904.

22. Gee M, Tahamont M, Flynn J, et al: Prostaglandin E_1 prevents increased lung microvascular permeability during intravascular complement activation in sheep. *Circ Res* 1987;61:420-428.

23. Gillespie M, Moore G, Wright E, et al: Salutary effects of prostaglandin E_1 in perfused rat lungs injured with hydrogen peroxide. *J Pharmacol Exp Ther* 1987;241:1-5.

24. Duara S, Fox W: Persistent pulmonary hypertension of the neonate, in Thibeault D, Gregory G (eds): *Neonatal Pulmonary Care*. East Norwalk, Conn, Appleton-Century-Crofts, 1986, p 466.

25. Csaba I, Sulyok E, Ertl T: Relationship of maternal treatment with indomethacin to persistence of fetal circulation syndrome. *J Pediatr* 1978;92:484.

26. Manchester D, Margolis H, Sheldon R: Possible association between maternal indomethacin therapy and primary pulmonary hypertension in the newborn. *Am J Obstet Gynecol* 1976;126:467-469.

27. Rudolph A: Effects of aspirin and acetaminophen in pregnancy and in the newborn. *Arch Intern Med* 1981;141:358-363.

28. Holcroft J, Vassar M, Weber C: Prostaglandin E_1 infusion and survival in patients with the adult respiratory distress syndrome. *Ann Surg* 1986;203:371-378.

29. Shoemaker W, Appel P: Effects of prostaglandin E_1 in adult respiratory distress syndrome. *Surgery* 1986;99:275-282.

30. Szczeklik J, Dubiel J, Mysik M, et al: Effects of prostaglandin E_1 on pulmonary circulation in patients with pulmonary hypertension. *Br Heart J* 1986;40:1397-1401.

31. Hyman A, Spannhake E, Kadowitz P: Prostaglandins and the lung. *Am Rev Respir Dis* 1978;117:111-135.

32. Swan P, Tibbals J, Duncan A: Prostaglandin E_1 in primary pulmonary hypertension. *Crit Care Med* 1986;14:72-73.

In Other AMA Journals

JAMA

Access to Medical Care for Black and White Americans

R. J. Blendon; L. H. Aiken; H. E. Freeman: C. R. Corey (*JAMA*. 1989;261:278)

Urinary Tract Infections and Circumcision

A Case-Control Study

Lynn W. Herzog, MD, MPH

• It has been shown that uncircumcised infants have a higher rate of urinary tract infections in the first few months of life. To investigate further the association between noncircumcision and urinary tract infections, a case-control study was performed of infant boys who had a catheterized or suprapubic urine culture done as part of an acute illness visit. Cases (n = 36) were those infants who had a positive culture (>105 organisms per milliliter); controls (n = 76) had a negative culture (<103 organisms per milliliter). There were no significant differences found in the two groups in age, ethnic group, and type of medical insurance. All of the cases were uncircumcised, vs 32% of controls. The data were analyzed separately by age, ethnic group, type of insurance, and method of culture, and in all groups the cases were significantly more likely to be uncircumcised. Of the 31 cases who underwent roentgenographic investigations, 8 had abnormal findings. Noncircumcision seems to be a highly significant risk factor for urinary tract infection in infants up to 12 months of age, affects infants regardless of race and socioeconomic status, and is associated with anatomic abnormalities in 26% of cases.

(*AJDC*. 1989;143:348-350)

Several recent studies have demonstrated a relationship between noncircumcision and urinary tract infections (UTIs) in young infants. Ginsburg and McCracken[1] first noted that 95% of male infants with UTI were uncircumcised. However, with no comparison group, they could not determine the significance of this finding. Wiswell et al,[2,3] in extensive retrospective cohort studies of US Army dependents, have documented that uncircumcised infants have a 10-fold to 20-fold greater risk of UTI in the first few months of life. Several aspects of this relationship need further study: Does the difference in incidence of UTI apply to older infants as well? Do ethnic, racial, or socioeconomic factors play a role? Are UTIs in the uncircumcised infants associated with urinary tract anomalies? The present study was performed to corroborate previous findings in a different group of patients, and to investigate the role of urinary tract anomalies, age, race, and socioeconomic status.

PATIENTS AND METHODS

We performed a retrospective case-control study of infants who had a urine culture done at The Children's Hospital, Boston, Mass. The study included all male infants under 12 months of age who had a suprapubic or catheterized urine culture done in the emergency department as part of the workup for an acute illness (including fever, gastrointestinal tract, or urinary tract symptoms). Patients were ascertained retrospectively by reviewing all urine cultures from the bacteriology laboratory for the years 1985 and 1986. *Cases* were defined as those patients who had a suprapubic (bladder tap) or catheterized urine culture that yielded more than 100 000 organisms per milliliter of a single species. *Controls* were those patients who had a negative suprapubic or catheterized urine culture (<1000 organisms per milliliter). Cultures that yielded 1000 to 100 000 organisms per milliliter were considered to contain possible contaminants and were analyzed separately. Infants with a previous UTI were excluded, as were those with a known urinary tract anomaly or myelodysplasia.

We reviewed the medical records of all patients to determine the circumcision status, racial/ethnic group, and type of medical insurance (as an approximation of socioeconomic status). When information on circumcision status was not in the record, the parents were contacted by letter for this information.

Statistical analysis was done by χ^2 or Fisher's Exact Test for categorical variables, and continuous variables were analyzed by the Mann-Whitney rank sum test, as they were not normally distributed.

RESULTS

There were 211 male infants from whom a catheterized or suprapubic urine culture was obtained. Fifty-nine infants were excluded because of anatomic problems, previous UTI, or equivocal culture results. Of the 152 remaining cultures, 37 were positive and 115 were negative. One case and 26 controls were excluded because their circumcision status could not be determined. In addition, 13 controls were excluded because their race could not be determined. The final total was 36 cases and 76 controls.

There was a highly significant difference in the frequency of circumcision between the cases and the controls. None of the 36 cases were circumcised, but 52 of the 76 controls were ($P<.0001$).

The data were analyzed separately by age, race, and type of insurance, and the results are shown in the Table. The mean age of the cases was 3.7 months and the mean age of the controls was 4.5 months (P was not significant by the Mann-Whitney rank sum test). Among the cases, 50% were more than 3 months of age, with the oldest being 10 months old. The difference in frequency of circumcision between cases and controls was highly significant for patients less than or more than 3 months old.

When the patients were separated by ethnic group, cases were significantly

Accepted for publication November 19, 1988.

From the Division of Ambulatory Pediatrics, The Children's Hospital, and the Department of Pediatrics, Harvard Medical School, Boston, Mass.

Presented in part at the Annual Meeting of the Ambulatory Pediatric Association, Washington, DC, May 3, 1988.

Reprint requests to Comprehensive Child Health Program, Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (Dr Herzog).

more likely to be uncircumcised among Hispanics ($P=.02$), blacks ($P<.0001$), and whites ($P=.0003$).

There was no significant difference between cases and controls in type of medical insurance. In each insurance group, cases were significantly more likely to be uncircumcised, as follows: Medicaid, $P<.0001$; Blue Cross/private insurance, $P<.0001$; and self-pay, $P=.01$.

Most of the cultures were catheterized specimens (77%) rather than suprapubic aspirations. There was no significant difference in the type of culture obtained in cases vs controls, in different racial groups, or in circumcised vs uncircumcised infants. The results were analyzed separately for catheterized and bladder-tap cultures and the results are shown in the Table. Cases were significantly more likely to be uncircumcised in both the suprapubic ($P=.02$) and catheterized ($P<.0001$) groups.

Percentage of Patients Uncircumcised in Case and Control Groups, by Age, Race, Type of Insurance, and Method of Culture

	Group		
	Cases, No. of Subjects (% Uncircumcised)	Controls, No. of Subjects (% Uncircumcised)	P
Total	36 (100)	76 (32)	<.0001
Age			
<3 mo	17 (100)	30 (36)	<.0001
>3 mo	19 (100)	46 (28)	<.0001
Race			
Hispanic	17 (100)	12 (67)	.02
Black	10 (100)	26 (27)	<.0001
White	7 (100)	36 (25)	.0003
Other	2 (100)	2 (0)	. . .
Insurance			
Blue Cross	12 (100)	33 (24)	<.0001
Medicaid	18 (100)	25 (40)	<.0001
Self-pay	6 (100)	18 (33)	.01
Method of culture			
Catheter	28 (100)	58 (26)	<.0001
Suprapubic	8 (100)	18 (50)	.02

Roentgenographic studies were done in 31 cases (86%) and consisted of a voiding cystourethrogram and either renal ultrasonography or an intravenous pyelogram. Most studies were done within one month of the infection. Eight subjects (26%) had anatomic abnormalities. Four had grade II reflux, two had grade IV reflux, one had posterior urethral valves and hydronephrosis, and one had ureteropelvic junction obstruction with hydronephrosis. The age of the patients with urinary tract anomalies ranged from 2 weeks to 8 months (median age, 7 weeks).

Blood cultures were done in 29 (80%) of the cases, and three (10%) were positive. In the controls, 53 blood cultures were done, and 1 was positive.

Seven (19%) of the 36 cases were not hospitalized. All but one of these patients were 6 months of age or older.

There were 27 patients (26 controls and 1 case) who were excluded from the study because information on circumcision status could not be obtained. Analysis of these patients showed that there was no significant difference between the excluded patients and all others in age, ethnic group, or type of specimen obtained.

If the definition of a clinically important culture is broadened to include colony counts higher than 10 000 colonies per milliliter of a single organism, the results do not change significantly. Five additional patients fit this criterion; two were circumcised. When these additional patients are included, 5% of cases were circumcised vs 68% of controls ($P<.0001$). All of the five additional patients had catheterized cultures. Results of roentgenographic studies were normal in all of the additional patients, making the frequency of anatomic abnormalities 22% (8/36).

There were an additional 10 patients who fit the study criteria and whose cultures yielded 1000 to 10 000 colonies per milliliter of a urinary pathogen (*Escherichia coli*, *Enterococcus*, and *Klebsiella*). Of these patients, 3 of 8 were circumcised (circumcision status unknown for two patients). Four patients had suprapubic aspirates and 6 had catheterized cultures. Five of the 10 patients were admitted; 4 underwent roentgenographic studies, and 1 patient had grade II reflux. One patient had *E coli* sepsis.

If all cultures with more than 1000 organisms per milliliter are included, cases are still significantly more likely to be uncircumcised than are controls (90% vs 32%; $P<.0001$). The odds ratio, which approximates the relative risk of UTI in the uncircumcised subjects, is 19.

To determine if any patients were being treated for a UTI without a catheterized or suprapubic culture being obtained, all positive urine cultures from clean-catch (bagged) specimens were reviewed. Four patients were found who were treated for UTI without a confirmatory bladder tap or catheterized specimen being obtained. Two patients were circumcised and two were uncircumcised.

COMMENT

The results show that male infants with a UTI are significantly more likely to be uncircumcised than are male infants without a UTI. This was true regardless of age, racial and ethnic group (black, white, and Hispanic), or socioeconomic status (as crudely determined by type of medical insurance). This confirms the findings of Wiswell et al,[2,3] who reported that uncircumcised infants had a 10-fold to 20-fold greater risk of UTI. In the present study, the odds ratio (calculated using infants with >10 000 organisms per milliliter) was 39. The higher relative risk in this study may be due to the fact that we included older infants who were not hospitalized. If infants with anatomic abnormalities are detected earlier in life because they are sicker, then older infants would be more likely to have noncircumcision as the only predisposing factor for infection.

The method used to obtain the culture may influence the rate of infection. The

initial study by Wiswell and colleagues,[2] in which 90% of cultures were from catheterized patients, showed a relative risk of 20. In their subsequent study,[3] in which 92% of cultures were from suprapubic aspirations, the relative risk was only 10. In the present study also, the results were more significant for catheterized cultures ($P<.0001$) than for suprapubic cultures ($P=.02$). Although it is often stated that any growth on a suprapubic or catheterized culture is indicative of infection,[4,5] Kunin[6] believes that a catheterized specimen yielding more than 100 000 organisms per milliliter is clinically important, but that lower counts require repeated collection. We used stringent criteria for a positive culture, as did Wiswell et al[2,3] and Ginsburg and McCracken,[1] excluding all cultures that yielded less than 100 000 organisms per milliliter, or more than one type of organism. Using these criteria, the number excluded as possible contaminants from the catheterized cultures was 30 (19%) of 154; the corresponding value for bladder-tap cultures was 8 (20%) of 40. If only those cultures that yielded gram-positive organisms or more than one type of organism are considered contaminants, then 10% of each type of culture was composed of contaminants.

To our knowledge, only one study has compared catheterized cultures with bladder-tap cultures in children. Pryles et al[7] studied 42 asymptomatic children undergoing surgery and found that low levels of contamination (<10 000 organisms per milliliter) are more common in catheterized cultures (20%) than in suprapubic cultures (5%). There were no data on true infection, as the subjects were asymptomatic children. In another study comparing catheterized with voided samples,[8] which included infants with UTI, none of the catheterized cultures from the 50 well children yielded more than 1000 organisms per milliliter; among the 16 infants with a UTI, 1 culture yielded only 10 000 organisms per milliliter.

Anatomic abnormalities of the urinary tract were found in 26% of the patients studied. The frequency of urinary tract anomalies in male subjects with UTI has been reported to range from 7% to 70%.[1,9-16] The wide variation in frequency reflects the different ages, types of patients studied, types of roentgenographic studies done, and definitions of what is abnormal. In newborns, the frequency of roentgenographic abnormalities is 47% to 68%[9,11,16]; in infants less than 1 year of age it has been reported to be 7%[1], 30%,[16] 40%,[10] and 70%[13]; and in male subjects of all ages it is 47%.[15] Circumcision status was not mentioned in these studies, but they were from countries where neonatal circumcision is not routine. In the only study from the United States, 95% of the male subjects were uncircumcised and 7% had urinary tract abnormalities.[1] In most studies, as in the present study, approximately one half of the abnormalities found were varying degrees of reflux. The incidence of reflux abnormalities in normal infants and children is believed to be approximately 1%.[17-19]

In summary, noncircumcision is a highly significant risk factor for UTI in infants up to 12 months of age. This was true for all racial and socioeconomic groups. One fourth of these infants had urologic abnormalities requiring prolonged medical follow-up.

References

1. Ginsburg CM, McCracken GH. Urinary tract infections in young infants. *Pediatrics*. 1982; 69:409-411.
2. Wiswell TE, Smith FR, Bass JW. Decreased incidence of urinary tract infection in circumcised male infants. *Pediatrics*. 1985;75:901-903.
3. Wiswell TE, Roscelli JD. Corroborative evidence for the decreased incidence of urinary tract infections in circumcised male infants. *Pediatrics*. 1986;78:96-99.
4. Marks MI. Cystitis. In: Feigin RD, Cherry JD, eds. *Textbook of Pediatric Infectious Diseases*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 1987:524-525.
5. Gonzales R, Michael A. Urinary tract infections. In: Behrman RE, Vaughan VC, Nelson WE, eds. *Nelson Textbook of Pediatrics*. 13th ed. Philadelphia, Pa: WB Saunders Co; 1987:1147-1148.
6. Kunin CM. *Detection, Prevention, and Management of Urinary Tract Infections*. 3rd ed. Philadelphia, Pa: Lea & Febiger; 1979:60.
7. Pryles CV, Atkin MD, Morse TS, Welch KJ. Comparative bacteriologic study of urine obtained from children by percutaneous suprapubic aspiration of the bladder and by catheter. *Pediatrics*. 1959;24:983-991.
8. Pryles CV, Luder D, Alkan MK. A comparative study of bacterial cultures and colony counts in paired specimens of urine obtained by catheter versus voiding from normal infants and infants with urinary tract infection. *Pediatrics*. 1961;27:17-29.
9. Drew JH, Acton CM. Radiological findings in newborn infants with urinary tract infection. *Arch Dis Child*. 1976;51:628-630.
10. Bourchier D, Abbott GD, Maling TMJ. Radiological abnormalities in infants with urinary tract infections. *Arch Dis Child*. 1984;59:620-624.
11. Bergstrom T, Larson H, Lincoln K, Winberg J. Studies of urinary tract infections in infancy and childhood, XII: eighty consecutive patients with neonatal infection. *J Pediatr*. 1972;80:858-866.
12. Littlewood JM. Sixty-six infants with urinary tract infection in the first month of life. *Arch Dis Child*. 1972;47:218-226.
13. Stansfeld JM. Clinical observations relating to incidence and aetiology of urinary tract infections in children. *Br Med J*. 1966;1:631-637.
14. Smellie JM, Normand ICS, Katz G. Children with urinary tract infection: a comparison of those with and without vesicoureteral reflux. *Kidney Int*. 1981;20:717-720.
15. Smellie JM, Hodson CJ, Edwards D, Normand ICF. Clinical and radiological features of urinary tract infection in childhood. *Br Med J*. 1964;2:1222-1226.
16. Winberg J, Andersen HJ, Bergstrom T, Jacobsson B, Larson H, Lincoln K. Epidemiology of symptomatic urinary tract infection in childhood. *Acta Paediatr Scand*. 1974;suppl 252:8-11.
17. Lich R, Howerton LW, Goode LS, Davis LA. The ureterovesical junction of the newborn. *J Urol*. 1964;92:436-438.
18. Jones BW, Headstream JW. Vesicoureteral reflux in children. *J Urol*. 1958;80:114-115.
19. Bailey RR. Vesicoureteric reflux in healthy infants and children. In: Hodson J, Kincaid-Smith P, eds. *Reflux Nephropathy*. New York, NY: Masson Publishing USA Inc; 1979:59-61.

In Other AMA Journals

JAMA

Child Molestation and Pedophilia

A. K. Fuller (*JAMA*. 1989;261:602)

THE BEST WAY TO COMBAT INFECTIOUS DISEASE IS TO SEE RED

Changes occur rapidly in the field of infectious diseases. The 1988 Report of the Committee on Infectious Diseases, commonly called the Red Book, offers important new information on a number of topics, including:

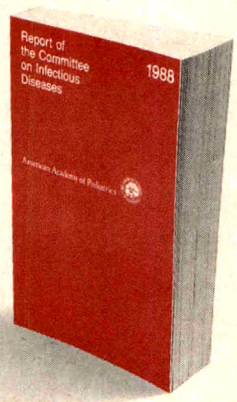
- Isolation precautions for hospitalized children
- Current guidelines on AIDS and HIV infections
- Children in day care
- New recommendations for hepatitis B
- Additional recommendations for pertussis
- New chapters on a variety of infectious diseases

The Red Book, published by the American Academy of Pediatrics, is one of the most respected pediatric reference manuals on infectious disease. It features 566 pages of infectious disease summaries, complete listings of reportable diseases, and state-by-state immunization laws, all efficiently organized.

The Red Book is just $25 for AAP members* and $30 for nonmembers. Hardbound copies are available for just $35 to members and $40 for nonmembers. Also available are reports of the task forces on pertussis and meningitis.

To get your copy of the Red Book, just call us toll free at 800/433-9016 (IL, 800/421-0589) to charge your order, or use the coupon.

*A complimentary copy has already been sent to all members of the Academy.



THE 1988 RED BOOK.

American Academy of Pediatrics

American Academy of Pediatrics
Publications Dept.
141 Northwest Point Blvd., P.O. Box 927
Elk Grove Village, IL 60009-0927

Please send me _____ copies of the Red Book ($25 for AAP members*, $30 for nonmembers. Hardbound edition is just $35 and $40, respectively. 1988, 566 pgs. ISBN 0-910761-20-5).

Also send _____ copies of the pertussis report ($6 for members, $25 for nonmembers) and _____ copies of the meningitis report ($6 for members, $15 for nonmembers).

Subtotal	_____
Handling charge per order	$3.50
Shipping (if applicable)	_____
TOTAL	_____

For every Red Book/pertussis report combination purchased, we'll include a meningitis report at no cost.

☐ Enclosed is my check/money order payable to the American Academy of Pediatrics. No shipping charges for prepaid, non-credit card orders.

For charge orders, complete the following or call toll free 800/433-9016 (IL, 800/421-0589). Shipping charges will be added to credit card orders.
Please charge my ☐ VISA ☐ MasterCard

_____

Exp. date _____

MC only, 4-digit # above bank name

_____

Please print:

Name _____

Address _____

City _____

State _____ Zip _____

Phone(____) _____

AAP member? _____ yes _____ no

ID number _____

_____

Signature

Allow 2-3 weeks for UPS delivery

All AAP members are sent one complimentary copy of the Red Book. Use this form to order additional copies and individual reports.

Advertisement

A NEW LOOK AT FORMULA ALLERGY AND INTOLERANCE: IS SOY EFFECTIVE?

Intestinal closure as an immunologic defense

As one of their many adaptations to the extrauterine environment, formula-fed neonates must also develop the ability to digest and absorb nutrition from ingested infant formula. This is no small task; it includes having to develop physiologic and immunologic defenses against the absorption of any of the more than 25 distinct, potentially allergenic proteins of cow's milk (notably beta-lactoglobulin, alpha-lactalbumin, and bovine serum albumin) or any of the four macromolecular soy proteins (notably glycinin). This maturational process is known as *intestinal closure.*

Breast milk is nutritionally and immunologically ideal, and, except for the occasional presence of intact allergens from the maternal diet, causes no problems for the immature intestinal mucosa. If, however, the infant ingests cow's milk- or soy-based formulas before intestinal closure can occur, the large intact proteins can flatten the villi[1,2] and/or cause them to atrophy, increasing the permeability of the lumen and rendering it more vulnerable to penetration by proteins that could provoke systemic or local hypersensitivity reactions, including eczema, asthma, diarrhea, and colic. In addition, episodes of gastroenteritis can damage mucosal surfaces, compromising the effectiveness of the barriers and leading to massive penetration by the allergens.[3] This increases the likelihood of further allergic manifestations.[4]

Early history good for soy protein . . .

Hill and Stuart[5] first proposed soybean preparations as a substitute for cow's milk in infant formulas in 1929. No allergic reactions to soy were recorded at the time, perhaps due to limited clinical experience, or perhaps because soy allergy may take weeks to develop, making soy-based formulas appear nonallergenic at the outset. In 1960 a series of case reports appeared citing gastrointestinal and "allergic" reactions to soy protein, followed by additional reports of soy protein intolerance concomitant with cow's milk protein intolerance, and positive intracutaneous tests of soybean protein in allergic children who received soy protein formula in infancy.[6]

. . . But soy may be as antigenic as cow's milk

Evidence is accumulating that sensitivity to soy is more widespread than was once believed, with estimates averaging around one fourth of infants who are sensitive to cow's milk,[7,8] but reaching as high as 40% of these infants.[9] Lothe et al[10] noted that 53% of colicky infants showed adverse reactions to soy protein formula. May et al[11] found that the feeding of soy protein formula from birth to 112 days did not lessen the antibody response to cow's milk protein products fed subsequently. A study by Eastham et al[4] also suggests that soy protein may be as antigenic as cow's milk protein. Thus there is evidence that soy protein formula may neither prevent the development of allergies nor resolve symptoms of cow's milk intolerance in many infants, and has been shown to prolong or aggravate these symptoms in some infants. For these reasons the American Academy of Pediatrics Committee on Nutrition (AAP/CON) recommends *against* the use of soy protein formulas in the dietary management of documented clinical allergic reaction to cow's milk protein, or in the routine management of colic. Instead, AAP/CON recommends protein hydrolysate formulas in these cases.[6]

Alternatives

Casein hydrolysate formula is hypoallergenic, but its expense (more than twice the price of routine formulas) prohibits routine use. Many parents also report that casein hydrolysate formulas smell and taste unpleasant.

A recently developed whey hydrolysate formula, however, may provide an economical alternative to soy for the management of colic or formula intolerance. As a routine formula, it can delay and may even prevent the development of allergy symptoms in infants at high risk due to a family history of atopy. This hydrolyzed whey protein formula is truly hypoallergenic, moderately priced for long-term or routine use, and has a pleasant taste and aroma. For a monograph on the new product, GOOD START H.A.™ Iron Fortified Hypoallergenic Infant Formula, write to Carnation Nutritional Products, ACS, 4144 Howard Ave, Kensington, MD 20895.

REFERENCES:

1. Halpin TC, Byrne WJ, Ament, ME: Colitis, persistent diarrhea and soy protein intolerance. *J Pediatr* 1977;91:404-407.
2. Ament ME, Rubin CE: Soy protein—another cause of the flat intestinal lesion. *Gastroenterology* 1972;62:227.
3. Iyngkaran N, Yadav M: Food Allergy, in Marsh MN (ed): *Immunopathology of the Small Intestine.* New York, John Wiley & Sons Ltd, 1987, p 421.
4. Eastham EJ, Lichauco T, Grady MI, et al: Antigenicity of infant formulas: Role of immature intestine on protein permeability. *J Pediatr* 1978;93(4):561-564.
5. Hill LW, Stuart HC: Soy bean food preparation for feeding infants with milk idiosyncrasy. *JAMA* 1929;93(13):985.
6. American Academy of Pediatrics Committee on Nutrition: Soy-protein formulas: Recommendations for use in infant feeding. *Pediatrics* 1983;72(3):359-363.
7. Bahna SL, Heiner DC: *Allergies to Milk.* New York, Grune & Stratton, 1980, p 127.
8. Businco L, Benincori N, Cantani A: Epidemiology, incidence and clinical aspects of food allergy. *Ann Allergy* 1984; 53:615-622.
9. Benkov KJ, LeLeiko NS: A rational approach to infant formulas. *Pediatr Ann* 1987;16(3):225-230.
10. Lothe L, Lindberg T, Jakobsson I: Cow's milk formula as a cause of infantile colic: A double-blind study. *Pediatrics* 1982;70:7-10.
11. May CD, Fomon SJ, Remigio L: Immunologic consequences of feeding infants cow milk and soy products. *Acta Paediatr Scand* 1982;71:43-51.

© 1988 Carnation Nutritional Products Printed in USA NP-009 9/88

The Use of Metalloporphyrins for the Chemoprevention of Neonatal Jaundice

David K. Stevenson, MD; Pamela A. Rodgers, PhD; Hendrik J. Vreman, PhD

• Decreasing bilirubin formation is an important strategy for the prevention of neonatal jaundice. The stannic porphyrins, in particular tin protoporphyrin and tin mesoporphyrin, have been proposed for this purpose because these compounds competitively inhibit heme oxygenase, the rate-limiting enzyme in the heme-degrading pathway. However, these compounds are not only potent inhibitors of heme oxygenase but are also photosensitizers, which can generate cytotoxic oxygen species, such as singlet oxygen. Therapeutic regimens designed to avoid the phototoxicity caused by these and other metalloporphyrins have been suggested. An alternative approach would be the development of derivatives of tin protoporphyrin or other heme analogs that are less phototoxic and are stronger inhibitors of heme oxygenase. However, our understanding of the molecular basis of heme oxygenase inhibition is still limited. The response of heme oxygenase to specific inhibitors varies a great deal and depends on the organ and stage of development. This may be a result of the differing proportions of heme oxygenase isoenzymes in different organs. These questions and others need to be systematically answered so we may better understand and treat disturbances in heme homeostasis. In addition, administration of these compounds may have other metabolic consequences directly and indirectly related to their potent, long-lasting inhibition of heme oxygenase. The significance of such effects, whether transient or permanent, needs to be elucidated.

(*AJDC* 1989;143:353-356)

Accepted for publication Oct 30, 1988.

From the Department of Pediatrics, Stanford (Calif) University School of Medicine.

Reprint requests to Department of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305-5119 (Dr Stevenson).

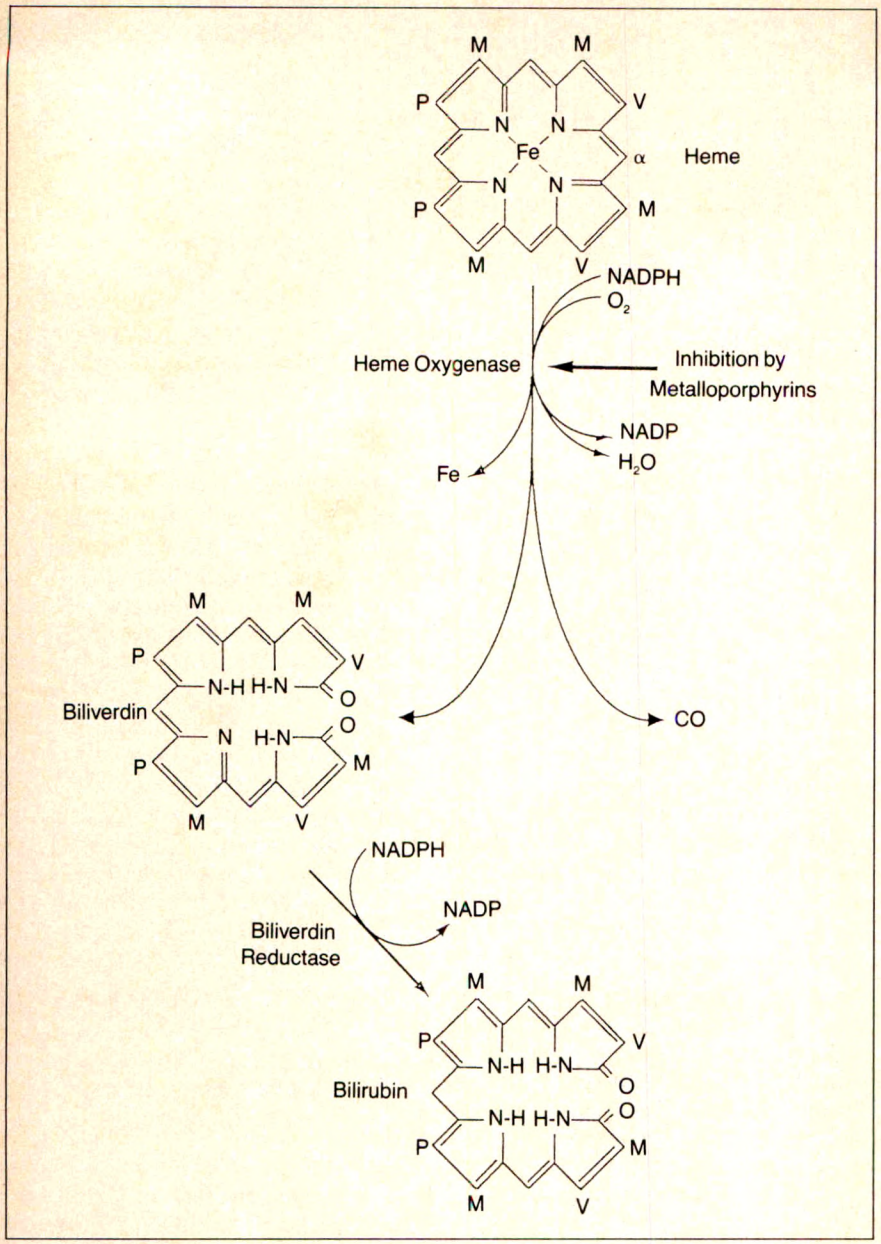
Human neonatal jaundice is a transitional phenomenon, resulting from the abrupt cessation of bilirubin clearance by the placenta and a transient deficiency of a specific hepatic glucuronosyltransferase system. Because bilirubin formation in the neonate is also increased compared with that in the adult (two to three times higher on a per-body-weight basis),[1] rapid accumulation of bilirubin occurs. Anything that further increases bilirubin production is very likely to exacerbate neonatal hyperbilirubinemia. Elevated production of the pigment has been associated with hemolysis, sequestered blood, polycythemia,[2] prematurity,[3,4] infants of diabetic mothers,[5] obstructive jaundice,[6] and certain racial groups.[7] The only common cause of neonatal jaundice, which is not primarily the result of accelerated bilirubin production, is breast milk feeding. Yet, both early- and late-onset breast milk jaundice syndromes may be exacerbated by increased bilirubin formation.

THE RATIONALE

Under normal conditions, approximately 80% to 90% of all bilirubin is produced by the breakdown of the heme derived from the senescing red blood cell hemoglobin. Only 10% to 20% derives from the heme of other globins, cytochromes, and hepatic hemoproteins.[8] An even greater proportion of bilirubin originates from the breakdown of hemoglobin heme under conditions that have been associated with pathologic bilirubin (see above). The first, rate-limiting step in the degradation of heme is catalyzed by the microsomal enzyme, heme oxygenase. When heme is bound to this enzyme in the presence of cytochrome P-450 reductase, reduced nicotinamide-adenine dinucleotide phosphate (NADPH), and oxygen, it catalyzes its own oxidative ring cleavage (Figure). The cleavage products, biliverdin and carbon monoxide, are produced in equimolar amounts. This step can be inhibited competitively by heme analogues, such as tin (Sn), zinc, chromium, and manganese metalloporphyrins. The carbon monoxide is bound to hemoglobin, and ultimately excreted in breath. Biliverdin is further reduced to bilirubin by the cytosolic enzyme, biliverdin reductase. The bilirubin thus produced is esterified by glucuronosyltransferase in the liver to monoglucuronosides and diglucuronosides and is excreted in the bile.

THE CHEMOPREVENTIVE APPROACH AND ITS CONSEQUENCES

Present clinical strategies to prevent excessive jaundice (plasma bilirubin level >205 μmol/L), which may lead to kernicterus, include prenatal maternal phenobarbital administration, phototherapy, and blood exchange transfusion (as a therapeutic last resort). A preventive approach may help to reduce hospital stay and may be of benefit in cases where phototherapy or exchange transfusion is not readily available. In the United States, where therapeutic options are generally available, the major advantage of the bilirubin production inhibitor approach is that only those infants who are high producers of the pigment and thus most likely to develop exaggerated jaundice refractory to phototherapy are treated, eg, those with immune-related hemolytic disease of newborn. Combined with a



Heme catabolic pathway.

sensitive and specific procedure to diagnose elevated bilirubin production from hemolysis (carbon monoxide detection in breath), the chemopreventive approach to neonatal jaundice represents the ideal clinical strategy: identify the individual at risk and prevent pathologic (eg, immune-related) jaundice before it occurs.

In view of the prominent role of increased bilirubin *formation* in all kinds of neonatal jaundice, the idea of inhibiting formation represents an experimental, strategic approach to the clinical problem. This approach was originally proposed by investigators at Rockefeller University, New York, who have studied metalloporphyrins as specific inhibitors of heme oxygenase for the chemoprevention of jaundice.[9] After nearly a decade of basic research, they selected stannic porphyrins as the most effective inhibitors and the results of the first clinical trial were published.[10] In this trial, Sn-protoporphyrin (SnPP) was used in the management of hyperbilirubinemia in term newborns with direct Coomb's-positive ABO incompatibility. The study established the efficacy of SnPP but raised questions with respect to the clinical importance of the effect (only a 31-μmol/L relative decrement in plasma bilirubin levels of treated infants was observed 72 to 96 hours after SnPP administration), mechanism of action, and safety (approximately 20% of infants receiving a total of three small doses of SnPP developed cutaneous erythema). The development of cutaneous erythema, although considered benign, provides telltale clinical evidence that the inhibitor acts also as a photoactive compound with intense absorption in the visible light range.

Commentaries on the first clinical trial have already been published.[11,12] However, some further remarks on the relevance of these research results to clinical pediatrics are worthwhile. First, the effect of SnPP was not clinically dramatic. Possible explanations for this could be that the drug dose was too small or that SnPP was not taken up by all the cell populations that form bilirubin. Furthermore, induction of heme oxygenase, which is a side effect of SnPP,[13] may partially compensate for its inhibition. Bilirubin could also be produced by a SnPP-insensitive pathway,[14] as has been observed in the rat intestine. Second, there is no direct proof that the decreased bilirubin levels were caused exclusively by inhibition of bilirubin production. This point is important, because SnPP is known to be an effective in vitro photosensitizer for the formation of singlet oxygen.[15] Porphyrin-sensitized photooxidations involve the production of an excited triplet state in the porphyrin, which can then react with biologic substrates, either directly (type 1 photooxygenation) through the production of free radicals or indirectly (type 2 photooxygenation) through the production of a singlet molecular oxygen.[16] Singlet oxygen is reportedly responsible for SnPP-enhanced photodegradation of bilirubin in vitro.[17] Are the in vitro photodegradative effects of SnPP relevant in the whole organism? The potential for enhanced in vivo photodegradation of bilirubin by SnPP has been demonstrated using the Gunn rat model.[18] Whether a similar phenomenon could occur in human neonates treated with SnPP at the lower doses used in the

recent clinical trial is unknown, but cannot be excluded by the information presented.

Furthermore, the proposed protective effect of albumin may be less pronounced in vivo as a consequence of the rapid plasma clearance of SnPP. This fact, which was reported in the first clinical trial, may indicate that SnPP is quickly distributed into tissues where the potential for photosensitivity could persist for days. The risk of phototoxicity might be greater in infants with impaired renal or hepatic function,[19] as the drug is excreted in urine and bile. Unfortunately, such impairment is common among premature or sick infants, precisely those who might benefit most from the inhibition of bilirubin formation. The phototoxic potential may be compounded by other therapeutic regimens such as oxygen therapy and phototherapy. The fact that some infants in the clinical trial demonstrated skin changes (transient erythema) consistent with dermal photosensitivity[20-22] is important to consider when comparing the risks and benefits of this proposed experimental therapy with those of the more standard therapies. Confidence in excluding other signs and symptoms, such as mild edema and the experience of itching or pain, is also limited in the neonate. Thus, a conservative position regarding the clinical use of SnPP or any other photoactive agent is that dermal and ocular photosensitivity have to be considered as potential undesirable side effects.

Strategies to avoid phototoxicity have been suggested.[10,23] One proposal involves limiting the light exposure to 450 nm only, thus avoiding excitation of the porphyrin to its triplet state and generation of singlet oxygen, which is cytotoxic and can damage membranes. Although possible, this approach is probably not practical because the complete avoidance of broad-spectrum light is unlikely, and the eventual exposure to powerful sunlight after discharge from the hospital could be injurious if SnPP were retained in tissues. A more desirable alternative would be the administration of SnPP derivatives or other heme analogues that are less phototoxic and are more potent inhibitors of heme oxygenase,[23,24] thus requiring lower doses for efficacy. One such derivative has already been introduced: Sn mesoporphyrin. Although Sn mesoporphyrin is ten times more potent an inhibitor than its parent compound, SnPP,[24] it is also potentially more phototoxic.[23] In general, the consideration of the use of such drugs requires further study, which should include an extensive photophysical and biodynamic characterization addressing the influence of route of administration, pharmacokinetics, wavelength intensity, duration of light exposure, the nature of the metal in the center of the porphyrin ring, the efficacy with which the porphyrin is converted by light to its triplet state, and the lifetime of the triplet state.

THE UNKNOWNS

Besides their potential for photosensitization, the metalloporphyrins may have other metabolic consequences, which were discussed in a recent review of heme oxygenase.[25] The identified inhibitors include Sn, zinc, chromium, and manganese protoporphyrins.[26,27] One of the more serious consequences of SnPP administration that has been reported is that of altered glutathione metabolism in the brain.[28] As a result of persistent inhibition of heme oxygenase, a number of metabolic perturbations are also possible. Drugs that alter heme oxygenase activity often affect heme synthesis and distribution into such hemoproteins as P-450. This suggests that these inhibitory metalloporphyrins have the potential to disturb not only heme homeostasis but also the drug metabolism capacity of the organism. In addition, the potential effect on iron metabolism is unknown. The repercussions of such effects, whether transient or permanent, need to be elucidated.

The parenteral administration of SnPP causes the elimination of heme in the bile.[29,30] However, the fate of heme reaching the intestine has not been adequately determined, particularly in the neonate. In addition, Hintz et al[14] have observed a lack of inhibition of adult and neonatal rat intestinal heme oxygenase by SnPP. The lack of inhibition is apparently not attributable to SnPP concentration in the intestine being low, compared with other inhibitable tissues. In fact, for a given dose, the tissue concentration of SnPP in the spleen (an inhibitable tissue) is not much different from that in the intestine.[31] Our studies also suggest that the bacterial breakdown of heme in the intestine is an important source of carbon monoxide production (and potentially of bilirubin production) in suckling animals not treated with antibiotics.[32,33] The bilirubin produced from excess heme in the gut could participate in enterohepatic circulation, particularly if intestinal sources of heme oxygenase remained uninhibited.

Other potentially inhibitory metalloporphyrins have been less thoroughly investigated. Zinc protoporphyrin is an effective inhibitor of heme oxygenase activity in vitro and in vivo[28] and decreases bilirubin formation as measured by carbon monoxide production.[33] It is reportedly capable of lowering plasma bilirubin levels in neonatal primates.[34] Manganese protoporphyrin is also a promising compound, having an inhibitory potential equal to zinc protoporphyrin and perhaps being a less potent photosensitizer than SnPP. Even though a fair number of metalloporphyrins and derivatives are being studied for their phototoxic properties toward tumor cells, only a limited number of compounds have been studied for efficacy of inhibiting heme oxygenase. The response of heme oxygenase to these inhibitors varies considerably and depends on the tissue and stage of development. This may be a consequence of the differing proportions of heme oxygenase isoenzymes in each organ.[35] Obviously, a greater understanding of the molecular basis of heme oxygenase inhibition and the potential metabolic repercussions of such inhibition is required before a complete evaluation of these drugs can be made.

THE CLINICAL RELEVANCE

Decreasing bilirubin formation is an important strategic goal for the prevention of neonatal jaundice. However, it is important that if the goal is to be reached, it is reached safely. It is currently possible to identify infants with increased bilirubin production within hours of the time of birth by estimating their carbon monoxide production, a proved index of bilirubin formation. The technique is noninvasive and easy to perform.[36] Although not widely used now, it could be used to identify the majority of infants without increased

bilirubin production, and unnecessary treatment could thus be avoided. On the other hand, infants at high risk for severe jaundice because of increased bilirubin production could be identified even before jaundice appeared clinically or plasma hemoglobin values began to drop. Such infants might be selected for therapy with a potent inhibitor of heme oxygenase activity that is minimally photoreactive. The safety of such an undertaking can only be ascertained through additional studies to elucidate the impact of such a compound on organ-specific heme metabolism. The chemopreventive approach is reasonable and tempting, and the power of this biochemical tool under experimental conditions has been demonstrated. Limited clinical efficacy has also been reported. However, taking the second step in the clinical arena is sometimes as hard as taking the first step,[37] and often harder, for different reasons. One of these reasons is the distance that was already traveled during the first step. The collective knowledge gained so far should at least make one stop and think about whether, when, how, and with what agent the next step should be taken.

This work was supported in part by a grant (RR-00081) from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health, Mead Johnson Nutritional Division, Evansville, Ind, and the Christopher Taylor Harrison Research Fund, Stanford, Calif.

References

1. Coburn RF, Blakemore WS, Forster RG: Endogenous carbon monoxide production in man. *J Clin Invest* 1963;42:1172-1178.
2. Bartoletti AL, Stevenson DK, Ostrander CR, et al: Pulmonary excretion of carbon monoxide in the human newborn infant as an index of bilirubin production: I. Effects of gestational and postnatal age and some common neonatal abnormalities. *J Pediatr* 1979;94:952-955.
3. Cohen RS, Ostrander CR, Cowan BE, et al: Pulmonary excretion rates of carbon monoxide using a modified technique: Differences between premature and full-term infants. *Biol Neonate* 1982;41:289-293.
4. Fischer AF, Ochikubo CG, Vreman HJ, et al: Carbon monoxide production in mechanically ventilated premature infants weighing less than 1500 g. *Arch Dis Child* 1987;62:1070-1072.
5. Stevenson DK, Bartoletti AL, Ostrander CR, et al: Pulmonary excretion of carbon monoxide in the human newborn infant as an index of bilirubin production: II. Infants of diabetic mothers. *J Pediatr* 1979;94:956-958.
6. Salomon WL, Vreman HJ, Kwong LK, et al: Red cell destruction and bilirubin production in adult rats with short-term biliary obstruction. *J Pediatr Gastroenterol Nutr* 1986;5:806-810.
7. Fischer AF, Nakamura H, Uetani Y, et al: Comparison of bilirubin production in Japanese and Caucasian infants. *J Pediatr Gastroenterol Nutr* 1988;7:27-29.
8. Berk PD, Jones EA, Howe RB, et al: Disorders of bilirubin metabolism, in Bondy PK, Rosenberg LE (eds): *Metabolic Control and Disease*, ed 8. Philadelphia, WB Saunders Co,1980, pp 1009-1088.
9. Drummond GS, Kappas A: Prevention of neonatal hyperbilirubinemia by Sn-protoporphyrin IX, a potent competitive inhibitor of heme oxidation. *Proc Natl Acad Sci USA* 1981;78:6466-6470.
10. Kappas A, Drummond GS, Manola T, et al: Sn-protoporphyrin use in the management of hyperbilirubinemia in term newborns with direct Coombs-positive ABO compatibility. *Pediatrics* 1988;81:485-497.
11. Stevenson DK, Vreman HJ: Sn-protoporphyrin: A consideration of the first clinical trial in human neonates. *Pediatrics* 1988;81:881-882.
12. Maisels MJ: Light vs tin? *Pediatrics* 1988;81:882-884.
13. Sardana MK, Kappas A: Dual control mechanism for heme oxygenase: Tin (IV)-protoporphyrin potently inhibits enzyme activity while markedly increasing content of enzyme protein in liver. *Proc Natl Acad Sci USA* 1987;84:2464-2468.
14. Hintz SR, Kim CB, Vreman HJ, et al: Lack of inhibition of intestinal heme oxygenase by antibiotics and tin protoporphyrin. *Pediatr Res* 1988;23:50-53.
15. Land EJ, McDonagh AF, McGarvey DJ, et al: Photophysical studies of tin (IV)-protoporphyrin: Potential phototoxicity of a novel chemotherapeutic agent for the prevention of neonatal jaundice. *Proc Natl Acad Sci USA* 1988;85:5249-5253.
16. Wharen RE, So S, Anderson RE, et al: Hematoporphyrin derivative photocytotoxicity of human glioblastoma in cell culture. *Neurosurgery* 1986;19:495-501.
17. McDonagh AF, Palma LA: Tin-protoporphyrin: A potent photosensitizer of bilirubin destruction. *Photochem Photobiol* 1985;42:261-264.
18. McDonagh AF, Huang W: Phototoxicity of tin-protoporphyrin, abstracted. *Photochem Photobiol* 1987;45:102S.
19. Kearns GL, Williams BJ, Timmons OD: Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985;107:796-798.
20. Poh-Fitzpatrick MB: Molecular and cellular mechanisms of porphyrin photosensitization. *Photodermatology* 1986;3:148-157.
21. Rask EN, Howell WH: The photodynamic action of hematoporphyrin. *Am J Physiol* 1928;84:363-377.
22. Hawkins CW, Bickers DR, Mukhtar H, et al: Cutaneous porphyrin photosensitization: Murine ear swelling as a marker of the acute response. *J Invest Dermatol* 1986;86:638-642.
23. Delaney JK, Mauzerall D, Drummond GS, et al: Photophysical properties of Sn-porphyrins: Potential clinical implications. *Pediatrics* 1988;81:498-504.
24. Drummond GS, Galbraith RA, Sardana MK, et al: Reduction of the C_2 and C_4 vinyl groups of Sn-protoporphyrin to form Sn-mesoporphyrin markedly enhances the ability of the metalloporphyrin to inhibit in vivo heme catabolism. *Arch Biochem Biophys* 1987;255:64-74.
25. Maines MD: Heme oxygenase: Function, multiplicity, regulatory mechanisms, and clinical applications. *FASEB J* 1988;2:2557-2568.
26. Kappas A, Drummond GS, Simionatto CS, et al: Control of heme oxygenase and plasma levels of bilirubin by a synthetic heme analogue, tin-protoporphyrin. *Hepatology* 1984;4:336-341.
27. Maines MD: Zinc-protoporphyrin is a selective inhibitor of heme oxygenase activity in the neonatal rat. *Biochem Biophys Acta* 1981;673:339-350.
28. Maines MD: Effect of zinc- and tin-protoporphyrin on glutathione metabolism in rat organs, in Rand MJ, Raper C: *Pharmacology: Proceedings of the Tenth International Congress of Pharmacology.* Amsterdam, Elsevier Science Publishers, 1987, pp 809-815.
29. Kappas A, Simionatto CR, Drummond GS, et al: The liver excretes large amounts of heme into the bile when heme oxygenase is inhibited competitively by Sn-protoporphyrin. *Proc Natl Acad Sci USA* 1985;82:986-900.
30. Hintz SR, Kwong LK, Vreman HJ, et al: Recovery of exogenous heme as carbon monoxide and biliary heme in adult Wistar rats after tin protoporphyrin treatment. *J Pediatr Gastroenterol Nutr* 1987;6:302-306.
31. Anderson KE, Simionatto CS, Drummond GS, et al: Disposition of tin-protoporphyrin and suppression of hyperbilirubinemia in humans. *Clin Pharmacol Ther* 1986;39:510-520.
32. Posselt AM, Kwong LK, Vreman HJ, et al: Suppression of carbon monoxide excretion rate by tin protoporphyrin. *AJDC* 1986;140:147-150.
33. Hamori CJ, Vreman HJ, Rodgers PA, et al: Zinc protoporphyrin inhibits CO production in rats. *J Pediatr Gastroenterol Nutr*, in press.
34. Qato MK, Maines MD: Prevention of neonatal hyperbilirubinemia in nonhuman primates by Zn-protoporphyrin. *Biochem J* 1985;226:51-57.
35. Cruse I, Maines MD: Evidence suggesting that two forms of heme oxygenase are products of different genes. *J Biol Chem* 1988;263:3348-3353.
36. Smith DW, Inguillo D, Martin D, et al: Use of noninvasive tests to predict significant jaundice in full-term infants: Preliminary studies. *Pediatrics* 1985;75:278-280.
37. Lucey JF: A new era in therapy for hyperbilirubinemia. *Pediatrics* 1988;81:579.

In Other AMA Journals

JAMA

Harmful Genital Care Practices in Children

M. E. Herman-Giddens, N. L. Berson (*JAMA.* 1989;261:577)

Articles

Home Oxygen Therapy for Chronic Lung Disease in Extremely Low-Birth-Weight Infants

Bonnie B. Hudak, MD; Marilee C. Allen, MD; Mark L. Hudak, MD; Gerald M. Loughlin, MD

• Chronic lung disease that requires prolonged oxygen therapy commonly complicates the recovery of extremely low-birth-weight infants (<1000 g). We report follow-up data through 18.5 ± 0.9 (mean ± SEM) months of age in 30 extremely low-birth-weight infants (birth weight, 783 ± 24 g; gestational age, 26.0 ± 0.3 weeks) who were discharged home receiving supplemental oxygen. Oxygen was prescribed to maintain arterial oxygen saturation at 95% or greater. At discharge, postconceptional age was 40.5 ± 0.6 weeks, and weight was 2220 ± 50 g. Duration of home oxygen therapy was 4.5 ± 0.5 months. The mean weight percentile increased from less than 5 to 23 between discharge and the last follow-up. All infants survived; only 6 required hospitalization for acute medical illnesses. We conclude that carefully supervised home oxygen therapy permits the safe early discharge of selected extremely low-birth-weight infants with chronic lung disease.

(*AJDC*. 1989;143:357-360)

Chronic lung disease is a significant cause of mortality, morbidity, and prolonged hospitalization in the extremely low-birth-weight (ELBW) infant (<1000 g). Recent evidence has suggested that optimal cardiopulmonary support of the older infant with chronic lung disease requires maintenance of arterial oxygen saturation (Sao_2) at 95% or greater.[1-3] Other reports have demonstrated that older infants with a history of chronic lung disease who are without an apparent oxygen requirement at rest may become hypoxemic during feeding and sleep.[4,5] The clinical application of these observations to the management of an increasing population of surviving ELBW infants will identify more infants as candidates for home oxygen therapy. For many such candidates, receiving oxygen at home provides a practical alternative to an extended neonatal intensive care unit (NICU) stay, with the potential for improved parent-infant interactions and substantial cost savings.

After discharge, infants with chronic lung disease are at risk for growth failure, developmental delay, recurrent respiratory infections, and frequent rehospitalizations. Although chronic hypoxemia may contribute to these morbidities, most previous reports have not demonstrated the efficacy of home oxygen therapy in reducing these complications.[6-9] However, using more stringent criteria for adequacy of oxygenation, Groothuis and Rosenberg[10] recently described a beneficial effect of home oxygen therapy on weight gain in a selected group of infants. We detail our follow-up through the duration of home oxygen therapy in 30 ELBW infants discharged from the NICU of The Johns Hopkins Hospital, Baltimore, Md, receiving supplemental oxygen. Our experience provides further evidence that scrupulous maintenance of adequate oxygenation (ie, $Sao_2 \geq 95\%$) is associated with a greater rate of weight gain and a lower incidence of morbidity than previously reported.

PATIENTS AND METHODS

Over a 2-year period from August 1984 to August 1986, 37 ELBW infants were discharged from the NICU at The Johns Hopkins Hospital receiving supplemental oxygen. Of these, 30 were followed up prospectively in a multidisciplinary clinic. All infants met the definition of chronic lung disease proposed by Bancalari et al[11]: a history of hyaline membrane disease requiring mechanical ventilation during the first week of life and the persistence of respiratory symptoms, abnormal chest roentgenogram, and oxygen requirement at 30 days of age.

Infants were discharged home receiving supplemental oxygen when they met the usual discharge criteria and demonstrated acceptable cardiorespiratory stability. The latter requirement included a resting oxygen flow rate of not greater than 0.5 L/min and, when necessary, a well-established diuretic regimen (usually chlorothiazide and spironolactone).

Each child was followed up by a primary physician and was seen every 1 to 2 months in our clinic as well. Data collected at each clinic visit included an interim history (interval illnesses, hospitalizations, medications, oxygen problems, use of oxygen), weight, height, heart rate, respiratory rate, physical examination results, and pulse oximetry study (N-100 or N-10, Nellcor Inc, Hayward, Calif). Percentiles for growth parameters were obtained using National Center for Health Statistics standards. Postnatal age was corrected for prematurity. Chest roentgenogram, arterial blood gas determinations, electrolyte measurements, hematocrit, and echocardiogram were done when indicated. Evaluations by a nutritionist, developmental pediatrician, respiratory therapist, and physical therapist were regularly performed.

Criteria for weaning oxygen included the following: (1) Sao_2 of 95% or greater at rest associated with a decreased oxygen flow rate, (2) no increase in heart rate with a decrease in the oxygen flow rate, and (3) appropriate interval growth. The Sao_2 was continuously monitored for 30 to 60 minutes. Infants were studied at rest, while feeding, and, when possible, during sleep. For infants with an adequate Sao_2 while breathing room air in the clinic, oxygen administration was usually continued during sleep for a 2- to 4-week period before it was completely discontinued. Because it was not always possible in the clinic setting to measure the Sao_2 during sleep, each child was reevaluated both 1 week and 1 month after oxygen was completely discontinued. If a child was discharged from the clinic prior to 1 year of age,

Accepted for publication December 1, 1988.

From the Eudowood Pediatric Respiratory Science Division (Drs B. Hudak and Loughlin) and the Eudowood Neonatal Pulmonary Division (Drs Allen and M. Hudak), Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md.

Reprint requests to CMSC 141, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205 (Dr B. Hudak).

follow-up data on growth, pulmonary status, and complications were obtained by written questionnaire from the primary physician when the child was 1 year old.

During the same 2-year time period, 62 ELBW infants were discharged without supplemental oxygen. The hospital records of these infants were reviewed retrospectively. For all infants, abstracted data included birth weight, gestational age, race, sex, duration of mechanical ventilation, and duration of oxygen therapy. In addition, discharge weight, diet, medications, and length of hospitalization were available for 41 of the infants who did not require supplemental oxygen.

Statistical analysis was performed using the two-tailed unpaired Student t test and χ^2 analysis with the Yates correction for normally distributed variables. The normal approximation to the Mann-Whitney test was used to compare parameters that were not normally distributed.[12] In all cases $P<.05$ was considered significant.

RESULTS

The survival rate to discharge among live-born ELBW infants at The Johns Hopkins Hospital during the 2-year period studied was 76%. However, chronic lung disease developed in 70% of the survivors, and 37% were discharged from the NICU receiving supplemental oxygen. Infants discharged receiving supplemental oxygen had a mean ±SEM gestational age of 26.0±0.3 weeks and a mean birth weight of 783.0±24.5 g (Table 1). There was a higher proportion of both white ($P<.05$) and male ($P<.01$) infants among those who required oxygen at discharge.

Of the 30 infants followed up while receiving home oxygen, 29 were appropriately grown for gestational age, and one was small for gestational age. Six infants were the products of multiple gestations (5 twins, 1 triplet), but for each pregnancy only 1 infant met the criteria for inclusion in the study.

The infants discharged home receiving oxygen required mechanical ventilation for 54±4 days, a fraction of inspired oxygen of 0.5 or greater for 17±3 days, and a fraction of inspired oxygen of 0.3 or greater for 55±6 days. All of these requirements were greater than those for ELBW infants who did not require supplemental oxygen at discharge ($P<.01$).

At the time of discharge from the NICU (Table 2), the home oxygen group had a mean weight of 2200 g at 40.5 weeks postconceptional age and an average length of hospitalization of 102 days. These figures were similar to those for infants not discharged home receiving supplemental oxygen. Fifty-seven percent (17/30) of the oxygen-dependent infants were discharged receiving concentrated formula and with fluid restrictions, and 43% (13/30) were receiving diuretics. Oxygen requirements ranged from 0.125 L/min administered only with feedings to 0.5 L/min at rest, which was increased to 1 L/min with feedings.

Follow-up information at 1 year of age was available for all study infants, either by clinic visit (n=19) or by completion of a written questionnaire by the primary physician (n=11). The age at last follow-up was 18.5±0.9 months, with a range of 12 to 30 months. No children were receiving supplemental oxygen at their last follow-up. The mean length of time receiving home oxygen therapy after discharge from the NICU was 4.5 months (range, 2 weeks to 17 months).

Six infants receiving oxygen at home required a total of 9 rehospitalizations for acute medical illnesses through the last follow-up. Only 4 rehospitalizations occurred within the first 2 months after discharge, and 7 occurred while oxygen was still in use. Two infants required admission to the pediatric intensive care unit, and 1 required mechanical ventilation. Diagnoses on readmission included wheezing with or without accompanying pulmonary infection (n=7), pulmonary edema (n=1), and pneumonia (n=1). One third (10/30) of the infants had at least one episode of wheezing that improved in response to bronchodilators. Four infants with wheezing accounted for 7 readmissions. An additional 4 infants required hospitalization for surgical procedures: inguinal herniorrhaphy (n=3) and ventriculoperitoneal shunt revision (n=1).

Developmental follow-up information was available at 1 year of age for 77%

Table 1.—Comparison of Extremely Low-Birth-Weight Infants Discharged Home With and Without Supplemental Oxygen

	No Oxygen (N=62)	Home Oxygen (N=30)	P*
Birth weight, g†	821.5±16.5	783.0±24.5	NS
Gestational age, wk†	27.1±0.2	26.0±0.3	<.01
Race, No. of infants			
B	46	15	<.05
W	16	15	
Sex, No. of infants			
M	25	21	<.01
F	37	9	
Maternal age, y†	24.6±0.9	26.4±1.0	NS

*NS indicates not significant.
†Values are mean±SEM.

Table 2.—Status of Extremely Low-Birth-Weight Infants at Discharge

	No Oxygen (N=41)	Home Oxygen (N=30)	P*
Discharge weight, kg†	2.05±0.04	2.22±0.05	NS
Postconceptional age at discharge, wk†	39.6±0.8	40.5±0.6	NS
Length of hospital stay, d†	87.6±5.6	101.6±4.3	NS
Fluid restriction, No. (%) of infants	8/41 (20)	17/30 (57)	<.001
Medications, No. (%) of infants			
Diuretics	2/41 (5)	13/30 (43)	<.001
Bronchodilators	1/41 (2)	2/30 (7)	NS

*NS indicates not significant.
†Values are mean±SEM.

Table 3.—Catch-up Growth of Extremely Low-Birth-Weight Infants Discharged Home Receiving Supplemental Oxygen

Weight Percentile	No. of Infants		
	Discharge From NICU*	Supplemental Oxygen Stopped	Last Follow-up
<5%	23	10	7
5%-24%	7	1	10
25%-49%	0	5	8
≥50%	0	3	5

*NICU indicates neonatal intensive care unit.

(23/30) of the study infants. No significant handicap was found in 19 (83%) of the 23 infants examined: 6 (26%) were normal; 5 (22%) had normal cognition, with motor examination results that were suspicious for minor neuromotor dysfunction; 8 (35%) had definite evidence of minor neuromotor dysfunction; and 4 (17%) had multiple handicaps (all 4 had cerebral palsy and mental retardation, 1 was blind, and another had moderate to severe sensorineural hearing loss).

Many infants receiving oxygen at home achieved catch-up growth that coincided with recovery from their lung disease and the weaning of supplemental oxygen (Table 3). At discharge from the NICU, 23 of 30 infants had weights below the 5th percentile for corrected age. Only 10 remained below the 5th weight percentile at the time supplemental oxygen was discontinued. At the last follow-up, the mean weight percentile was 23, and 7 infants remained below the 5th percentile. Of these 7 infants, factors potentially responsible for poor growth were identified in six; 2 had significant neurodevelopmental handicaps, 2 had behavioral problems associated with feeding, 1 had been small for gestational age at birth, and 1 had home oxygen therapy stopped against medical advice.

No deaths occurred among the group of infants discharged home receiving oxygen. There were no significant problems attributable to the presence of oxygen in the home.

During the study period seven infants were discharged receiving supplemental oxygen but were not followed up in our clinic. Five of these infants were transferred from the NICU to a long-term–care facility for children; two had their follow-up elsewhere. At 1 year of age (mean ± SEM, 17.7 ± 1.9 months), all were alive. Six were breathing room air by 6.4 ± 2.0 months after discharge from the NICU, and one continued to receive oxygen at night at 22 months of age to treat severe obstructive sleep apnea. Four were treated for wheezing, and three required rehospitalization.

COMMENT

This study demonstrates that with scrupulous attention to adequacy of oxygenation, ELBW infants with a persistent oxygen requirement can be discharged home near term and can achieve satisfactory growth and development without incurring frequent rehospitalizations. Despite their extreme prematurity and the severity of their lung disease, these infants achieved better weight gain and had fewer complications than have been reported for infants of comparable birth weights discharged without supplemental oxygen[13-15] or infants of greater birth weights discharged home receiving supplemental oxygen.[6-9]

In previous reports infants have been discharged receiving supplemental oxygen if their Pa_{O_2} or transcutaneous P_{O_2} was less than 50 to 55 mm Hg while breathing room air.[6-9] Our criteria for using supplemental oxygen were more conservative, because we attempted to maintain the Pa_{O_2} within the normal physiologic range. Consequently, we discharged infants receiving supplemental oxygen if their Sa_{O_2} while breathing room air was not maintained at 95% or more (corresponding to a Pa_{O_2} ≥70 mm Hg[16]) at rest and during feeding and sleep. Depending on the results of a thorough predischarge pulse oximetric study, different oxygen flow rates were often prescribed for periods of rest, feeding, and sleep. Because hyperoxia has been implicated as one factor in the pathogenesis of retinopathy of prematurity, care was taken to prescribe the minimum oxygen flow rate that maintained the Sa_{O_2} at 95%; however, over the range of postconceptional ages at discharge in this study, most of the infant retina (with the possible exception of the temporal ora) is fully vascularized.[17] Only 1 of 30 infants had stage III retinopathy of prematurity detected by thorough serial ophthalmologic examination prior to discharge.

Recent characterizations of the pulmonary vascular response to oxygen in infants with chronic lung disease strongly support this more stringent criterion for adequacy of oxygenation. Several studies have shown that the pulmonary vascular resistance in infants with chronic lung disease is extremely sensitive to small changes in the Sa_{O_2}.[1-3] Mean pulmonary artery pressures[2,3] and right systolic time intervals[1] continued to decline with increasing supplemental oxygen until the Sa_{O_2} increased to 94% to 95%[2,3] or the Pa_{O_2} rose above 62 mm Hg,[1] respectively.

Maintenance of the Pa_{O_2} within the normal physiologic range (as inferred from an Sa_{O_2} ≥95%) may improve growth. Although attention has focused on increased oxygen and energy requirements[18,19] and on feeding disturbances resulting in inadequate energy intake[20] as the principal causes of poor weight gain in infants with chronic lung disease, subtle hypoxemia may be a more important direct and/or indirect factor. In their report on 22 infants with chronic lung disease who required supplemental oxygen to maintain an Sa_{O_2} greater than 92% and/or a transcutaneous P_{O_2} greater than 55 mm Hg, Groothuis and Rosenberg[10] found subnormal rates of weight gain only in the 7 infants in whom oxygen therapy was inappropriately discontinued. All 7 infants attained a normal rate of weight gain when oxygen therapy was resumed. We have also described substantial catch-up growth in our study infants. In contrast, no catch-up growth was reported in two studies in which less-stringent criteria for oxygenation were used.[6,7]

McCormick et al[21] found that 38% of infants with birth weights below 1500 g required at least one rehospitalization in the first year of life. Readmission has been reported even more frequently (43% to 66%) in infants who require oxygen at discharge—multiple admissions for individual infants are common.[6-8] One third (10/30) of our infants were rehospitalized, but only 20% (6/30) required readmission for acute medical illnesses, and only 10% (3/30) were admitted more than once.

We had previously noted sleep hypoxemia in older infants with chronic lung disease who had an adequate Sa_{O_2} while awake.[5] Based on these findings, most infants were given oxygen during sleep for 2 to 4 weeks before oxygen was discontinued completely. Recently, Garg et al[4] also described unsuspected hypoxemia, with the Sa_{O_2} decreasing below 80% during feeding and sleep in infants with chronic lung disease.

Increased rates of sudden death have been reported in infants with bronchopulmonary dysplasia.[22] Garg et al[23] recently reported the hypoxic arousal response of 12 infants with chronic lung disease who were not oxygen-dependent. Although 11 infants demonstrated an initial arousal response, significant apnea and/or bradycardia developed in all of them, and some required resuscitation. For these reasons, we used cardiorespiratory monitors for all infants until approximately 1 month after home oxygen therapy was discontinued.

As with other reports,[24,25] home oxygen therapy for our study infants was cost-effective. Using 1987 figures, inpatient and outpatient expenses for an infant receiving supplemental oxygen were $525/d and $30/d, respectively, resulting in an average potential savings of $66 825 per patient over 4.5 months of home oxygen therapy.

We have demonstrated that careful supervision of home oxygen therapy is safe and cost-effective for ELBW infants with chronic lung disease. The maintenance of Pa_{O_2} in the normal physiologic range (as inferred from a pulse oximetric $Sa_{O_2} \geq 95\%$) promotes normal growth and minimizes complications in the ELBW infant after discharge. The selection of infants for home oxygen therapy should be based on the fulfillment of general NICU discharge criteria; the establishment of a stable oxygen, diuretic, and nutritional regimen; and a demonstration that the parents are competent to care for the infant.

Dr B. Hudak is a fellow of the American Lung Association of Maryland.

References

1. Halliday HL, Dumpit FM, Brady JP. Effects of inspired oxygen on echocardiographic assessment of pulmonary vascular resistance and myocardial contractility in bronchopulmonary dysplasia. *Pediatrics*. 1980;65:536-540.
2. Abman SH, Wolfe RR, Accurso FJ, Koops BL, Bowman CM, Wiggins JW Jr. Pulmonary vascular response to oxygen in infants with severe bronchopulmonary dysplasia. *Pediatrics*. 1985;75:80-84.
3. Goodman G, Perkin RM, Anas NG, Sperling DR, Hicks DA, Rowen M. Pulmonary hypertension in infants with bronchopulmonary dysplasia. *J Pediatr*. 1988;112:67-72.
4. Garg M, Kurzner SI, Bautista DB, Keens TG. Clinically unsuspected hypoxia during sleep and feeding in infants with bronchopulmonary dysplasia. *Pediatrics*. 1988;81:635-642.
5. Loughlin GM, Allen PR, Pyzik P. Sleep related hypoxemia in children with bronchopulmonary dysplasia and adequate oxygen saturation awake. Presented at the Fifth International Congress of Sleep Research; June 28, 1987; Copenhagen, Denmark.
6. Abman SH, Accurso FJ, Koops BL. Experience with home oxygen in the management of infants with bronchopulmonary dysplasia. *Clin Pediatr*. 1984;23:471-476.
7. Daily DK. Home oxygen therapy for infants with bronchopulmonary dysplasia: growth and development. *Perinatol Neonatol*. 1987;11:26-35.
8. Koops BL, Abman SH, Accurso FJ. Out-patient management and follow-up of bronchopulmonary dysplasia. *Clin Perinatol*. 1984;11:101-122.
9. Campbell AN, Zarfin Y, Groenveld M, Bryan MH. Low flow oxygen therapy in infants. *Arch Dis Child*. 1983;58:795-798.
10. Groothuis JR, Rosenberg AA. Home oxygen promotes weight gain in infants with bronchopulmonary dysplasia. *AJDC*. 1987;141:992-995.
11. Bancalari E, Abdenour GE, Feller R, Gannon J. Bronchopulmonary dysplasia: clinical presentation. *J Pediatr*. 1979;95:819-823.
12. Zar JH. *Biostatistical Analysis*. 2nd ed. Englewood Cliffs, NJ: Prentice Hall International Inc; 1984.
13. Yu VYH, Orgill AA, Lim SB, Bajuk B, Astbury J. Growth and development of very low birthweight infants recovering from bronchopulmonary dysplasia. *Arch Dis Child*. 1983;58:791-794.
14. Kimble KJ, Ariagno RL, Stevenson DK, Sunshine P. Growth to age 3 years among very low-birth-weight sequelae-free survivors of modern neonatal intensive care. *J Pediatr*. 1982;100:622-624.
15. Pape KE, Buncic RJ, Ashby S, Fitzhardinge PM. The status at two years of low-birth-weight infants born in 1974 with birth weights of less than 1001 gm. *J Pediatr*. 1978;92:253-260.
16. Ramanathan R, Durand M, Larrazabal C. Pulse oximetry in very low birth weight infants with acute and chronic lung disease. *Pediatrics*. 1987;79:612-617.
17. Flynn JT. Retinopathy of prematurity. *Pediatr Clin North Am*. 1987;34:1487-1516.
18. Kurzner SI, Garg M, Bautista DB, Sargent CW, Bowman CM, Keens TG. Growth failure in bronchopulmonary dysplasia: Elevated metabolic rates and pulmonary mechanics. *J Pediatr*. 1988;112:73-80.
19. Weinstein MR, Oh W. Oxygen consumption in infants with bronchopulmonary dysplasia. *J Pediatr*. 1981;99:958-960.
20. Lifschitz MH, Seilheimer DK, Wilson GS, Williamson WD, Thurber SA, Desmond MM. Neurodevelopmental status of low birth weight infants with bronchopulmonary dysplasia requiring prolonged oxygen supplementation. *J Perinatol*. 1987;7:127-132.
21. McCormick MC, Shapiro S, Starfield BH. Rehospitalization in the first year of life for high-risk survivors. *Pediatrics*. 1980;66:991-999.
22. Werthammer J, Brown ER, Neff RK, Taeusch HW. Sudden infant death syndrome in infants with bronchopulmonary dysplasia. *Pediatrics*. 1982;69:301-304.
23. Garg M, Kurzner SI, Bautista D, Keens TG. Hypoxic arousal responses in infants with bronchopulmonary dysplasia. *Pediatrics*. 1988;82:59-63.
24. Pinney MA, Cotton EK. Home management of bronchopulmonary dysplasia. *Pediatrics*. 1976; 58:856-859.
25. Donn S. Cost effectiveness of home management of bronchopulmonary dysplasia. *Pediatrics*. 1982;70:330-331.

In Other AMA Journals

JAMA

Routing a Modern Pied Piper of Lamelin

D. E. Greydanus (*JAMA*. 1989;261:99)

Gastrointestinal Milk Intolerance of Infancy

Stuart Berezin, MD; Steven M. Schwarz, MD; Mark Glassman, MD; Marianna Davidian, MD; Leonard J. Newman, MD

• During a period of 30 months, cow's milk– or soy protein–induced colitis was diagnosed in 22 infants. All patients presented with hematochezia. Only three patients had substantial diarrhea. Colonoscopic evaluations demonstrated a characteristic mucosal appearance, manifested by aphthoid ulcerations with intervening, normal-appearing mucosa. Histologic findings included surface ulcerations and associated inflammation of the lamina propria and submucosa, marked by substantial eosinophilic infiltration. Both clinical symptoms and colonoscopic abnormalities rapidly resolved in all patients after the elimination of cow's milk and/or soy protein from the diet. These data indicate that hematochezia may be the predominant symptom of cow's milk protein and soy protein intolerance in many affected infants, and that colonoscopy is the most effective means of establishing a definitive diagnosis in this patient population.

(*AJDC* 1989;143:361-362)

Intolerance to cow's milk and/or soy protein has been implicated in the pathogenesis of diverse symptom complexes in infancy, including colic,[1] enterocolitis,[2] and anaphylaxis.[3] Although various testing procedures have been suggested to diagnose milk intolerance,[4] observation of symptoms after withdrawal and rechallenge of the suspected protein remains the sole reliable diagnostic technique.[5] To better define both the characteristics at presentation and the clinical course related to milk protein intolerance, we prospectively evaluated a group of infants with a presumptive diagnosis of cow's milk and/or soy protein intolerance.

PATIENTS AND METHODS

Over a 30-month period, 22 infants referred to the Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Valhalla, were diagnosed as having milk protein intolerance. Patients ranged in age from 2 to 16 weeks (mean ± SD, 6.73 ± 4.97 weeks), and were free of associated neonatal problems. Hematochezia was present in all infants; however, substantial diarrhea (>30 g/kg/d) occurred in only three patients. At the time of presentation, 15 infants were receiving either cow's milk (11 infants) or soy protein (four infants) exclusively, and five patients were breast-fed (with soy formula supplementation in one infant). All mothers of breast-fed infants had a history of cow's milk ingestion during lactation. Two subjects were fed both cow's milk and soy protein formulas in the week before the onset of symptoms, and no infant had yet received solid food. At initial presentation, the following laboratory tests were performed: complete blood cell count, platelet count, prothrombin and partial thromboplastin time determinations, total serum protein and albumin level measurements, and quantitative IgE and IgE antibody level measurements (cow's milk, soy). Two stool cultures for *Salmonella*, *Shigella*, *Campylobacter* subspecies *jejuni*, *Clostridium difficile*, and enterohemorrhagic *Escherichia coli*, two stool samples for rotavirus culture, and three stool specimens for ova and parasite cultures were obtained in all cases. If cultures were negative, the nature and extent of colonic involvement was determined by colonoscopic examination, including multiple biopsies, using a flexible fiberoptic sigmoidoscope. All procedures were recorded on videotape for subsequent review and comparison with later studies (see below). In preparation for colonoscopy, routine formula and/or breast-feeding was discontinued four hours before the procedure, and an infant glycerine suppository was given two hours before the examination. Informed written consent was obtained from the legal guardian of each patient. This protocol had the approval of the Institutional Review Board (Committee for the Protection of Human Subjects), New York Medical College.

RESULTS

In all infants studied, the mean (± SD) hematocrit was 0.37 ± 0.07. Hypoproteinemia and/or clotting abnormalities were not demonstrated in any patient. Eosinophilia with a cell count greater than $0.3 \times 10^9/L$[6] was noted in four patients, an elevated IgE level[7] was found in six patients, and a positive radioallergosorbent test for cow's milk protein was determined in two infants. All stool cultures for bacterial pathogens, ova, and parasites as well as rotavirus were negative. As shown in Fig 1, the appearance of the colonic mucosa during endoscopic examination demonstrated a characteristic pattern in all patients, marked by the presence of superficial aphthoid ulcerations surrounded by an erythematous margin. The intervening mucosa appeared normal. Typical lesions were observed in the rectosigmoid colon in 19 of 22 patients, and these abnormalities were found in the descending colon (with concomitant rectal sparing) in three of 22 infants. In all patients, aphthoid ulcerations were noted in both the transverse and ascending colon during the initial examination. In addition to these observations, nonspecific colonoscopic findings (patchy erythema, loss of normal vascular pattern) were described in 12 patients. Microscopic examination of biopsy specimens obtained at ulcer margins demonstrated superficial mucosal ulceration with epithelial cell loss. Abnormalities of the surrounding lamina propria and submucosa included varying degrees of acute and chronic inflammation; however, the predominant histopathologic abnormality was an inflammatory response with marked eosinophilic infiltration (Fig 2).

After the presumptive diagnosis of protein intolerance on the basis of clinical, laboratory, and characteristic colonoscopic findings, 19 of 22 infants began receiving a protein hydrolysate formula (Nutramigen, Bristol-Myers Inc, USPNG, Evansville, Ind). In every case, rectal bleeding ceased, confirmed by an absence of blood in the stool (Hemoccult, SmithKline Diagnostics Inc, Sunnyvale, Calif), within one week of institution of therapy. Repeated colonoscopy performed two weeks after the initiation of protein hydrolysate formula feedings demonstrated normal colonic mucosa. In three breast-fed infants, breast-feeding was continued. However, each mother was placed on a cow's milk protein-free diet.

Accepted for publication Nov 14, 1988.

From the Department of Pediatrics, Division of Gastroenterology and Nutrition (Drs Berezin, Schwarz, Glassman, Newman), and the Department of Pathology (Dr Davidian), New York Medical College, Valhalla.

Reprint requests to New York Medical College, Department of Pediatrics, Munger Pavilion, Valhalla, NY 10595 (Dr Berezin).

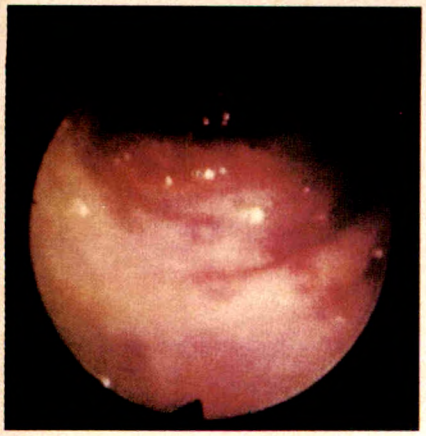


Fig 1.—Typical colonoscopic appearance in infant with suspected cow's milk protein intolerance. Note presence of aphthoid ulcerations with normal-appearing surrounding mucosa.

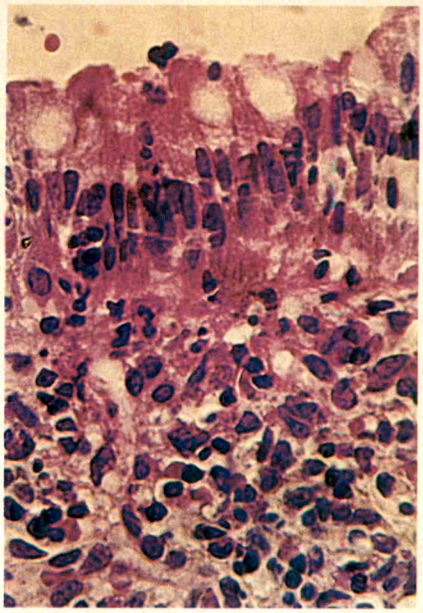


Fig 2.—Histologic section of colonic mucosa shows hyperplastic surface epithelium with inflammatory cell infiltrate and lamina propria with numerous eosinophils (hematoxylin-eosin, original magnification ×400).

Within two weeks, symptoms ceased in these infants. Two months after symptom resolution, 17 formula-fed infants were rechallenged with cow's milk or soy protein–based formula. In all cases, a recrudescence of the presenting clinical findings was heralded by the reappearance of blood in the stools. Repeated colonoscopies, limited to the descending colon, demonstrated characteristic mucosal abnormalities in all infants. In every case, symptom resolution and blood-free stools were rapidly achieved after reinstitution of the protein hydrolysate formula feedings.

COMMENT

The clinical findings in this group of infants establish the importance of biopsy-proved colitis in milk and/or soy protein intolerance. These data indicate that in affected infants presenting with hematochezia, aphthoid ulceration of the colonic mucosa may be a characteristic finding. Furthermore, in contrast with several earlier studies,[8-10] substantial diarrhea did not appear to be a major finding in our patient population. Criteria for establishing the diagnosis of milk protein intolerance remain somewhat controversial. Previously, both serologic and skin testing were shown to be of questionable value,[11] since abnormal results may fail to discriminate between protein allergy and atopy induced by other antigens.[12] The technique developed by Goldman et al,[5] which involves elimination and rechallenge with the suspected offending protein on three separate occasions, has been the most widely accepted method of establishing a diagnosis of food intolerance. The present results suggest that early colonoscopy in infants presenting with hematochezia without an obvious cause (eg, anal fissures, infection) is the most efficacious means of identifying a protein intolerant population. Although the appearance of the colonic mucosa seen in our patients, including histologic findings (mucosal ulceration, eosinophilic infiltration), may be similar in other disease states (eg, inflammatory bowel disease, Behçet's syndrome),[13] rapid resolution and reappearance of colonic abnormalities after withdrawal and rechallenge with the appropriate protein clearly establish a clinical diagnosis of protein intolerance. Of note is the fact that all infants tolerated colonoscopic evaluations without difficulty, and intravenous and/or intramuscular sedation were not required. In addition, minimal preparation, consisting of cessation of feedings four hours before the procedure and an infant glycerine suppository given two hours before colonoscopy, was sufficient to allow for adequate inspection of the colonic mucosa without interference from fecal material.

In the present study, infants who were breast-fed before clinical presentation experienced symptom resolution after withdrawal of cow's milk protein from the maternal diet, while the infants continued to breast-feed. These findings contrast somewhat with results in a similar group of infants, who experienced a highly variable response to maternal protein restriction under the same clinical conditions.[14] Thus, further evaluation of symptomatic, breast-fed infants will be required to establish a conclusive diagnosis of cow's milk protein intolerance in this group.

The results reported herein indicate that hematochezia may be a frequent clinical finding in infants presenting with milk protein intolerance. Obviously, since this study did not evaluate the total population of milk-intolerant infants, additional investigation will be required to determine the overall importance of these findings in patients who are allergic to protein. Nevertheless, the observation of characteristic colonic mucosal lesions in suspected cases may confirm the diagnosis of protein intolerance.

References

1. Lothe L, Lindberg T, Jakobsson I: Cow's milk formula as a cause of infantile colic: A double-blind study. *Pediatrics* 1982;70:7-10.
2. Gryboski JD: Gastrointestinal milk allergy in infants. *Pediatrics* 1966;38:354-362.
3. Lifschitz CH, Hawkins HK, Guerra C, et al: Anaphylactic shock due to cow's milk protein hypersensitivy in breast-fed infant. *J Pediatr Gastroenterol Nutr* 1988;7:141-144.
4. Eastham EJ, Walker WA: Adverse effects of milk formula ingestion on the gastrointestinal tract. *Gastroenterology* 1979;76:365-374.
5. Goldman AS, Anderson DW, Sellers WA, et al: Milk allergy: I. Oral challenge with milk and isolated milk proteins in allergic children. *Pediatrics* 1963;32:425-443.
6. Cunningham AS: Eosinophil counts: Age and sex differences. *J Pediatr* 1975;87:426-427.
7. Kjellman N: Predictive value of high IgE levels in children. *Acta Paediatr Scand* 1976;65: 465-471.
8. Jenkins HR, Pinicott JR, Soothill JF, et al: Food allergy: The major cause of infantile colitis. *Arch Dis Child* 1984;59:326-329.
9. Halpin TC, Byrne WJ, Ament ME: Colitis, persistent diarrhea and soy protein intolerance. *J Pediatr* 1977;91:404-410.
10. Whitington PF, Gibson R: Soy protein intolerance: Four patients with concomitant cow's milk intolerance. *Pediatrics* 1977;59:730-732.
11. Shapiro GG, Bierman CW, Furukoawa CT, et al: Allergy skin testing: Science or quackery? *Pediatrics* 1977;59:495-498.
12. Dannaeus A, Johansson SGO, Foucard T, et al: Clinical and immunological aspects of food allergy in childhood. *Acta Paediatr Scand* 1977;66:31-37.
13. Chong SKF, Wright VM, Nishigame T, et al: Infantile colitis: A manifestation of intestinal Behçet's syndrome. *J Pediatr Gastroenterol Nutr* 1988;7:622-627.
14. Lake AM, Whitington PF, Hamilton SR: Dietary protein–induced colitis in breast-fed infants. *J Pediatr* 1982;101:906-910.

Patterns of Cardiac Care in Infants With Down Syndrome

Daniel S. Schneider, MD; Kenneth G. Zahka, MD; Edward B. Clark, MD;
Catherine A. Neill, MD, FRCP(LOND); and the Baltimore-Washington Infant Study Group

• To determine if the pattern of cardiac care is affected by the presence of Down syndrome (DS) we analyzed the records of infants enrolled in the Baltimore-Washington Infant Study, a regional case-control study of congenital cardiovascular malformations. The age at cardiac diagnosis, the timing of cardiac surgery, and the one-year outcome were compared in 160 infants with DS and 540 infants with the same cardiac diagnoses but without chromosomal or other extracardiac anomalies (isolated cardiovascular malformation [ICM] group). Cardiac referral and diagnosis were accomplished by 13 weeks of age in 78% of infants with DS and 67% of those with ICMs. However, by 26 weeks of age, the proportion of infants in both groups was comparable. Cardiac surgery was performed before 1 year of age in 99 of 160 infants with DS and in 141 of 540 infants with ICMs. The surgical outcome was similar in the two groups. We conclude that for defects of comparable severity, the pattern of cardiac care in the Baltimore–Washington, DC, area for infants with DS is timely and comparable to care for infants with ICMs.

(*AJDC* 1989;143:363-365)

Congenital heart defects occur in 40% of infants with Down syndrome (DS), and they contribute considerably to the morbidity and mortality in these infants.[1] Previous studies have shown marked improvement in clinical status in patients with DS who survive cardiac surgery.[2] However, some have speculated that infants with DS and associated congenital heart defects receive unequal care compared with infants with isolated congenital cardiovascular malformations (ICMs).[3] To evaluate the impact of DS on the age at cardiac diagnosis and the timing of surgery, we identified infants with DS and congenital heart defects and compared them with infants with similar ICMs registered in the Baltimore-Washington Infant Study (BWIS).

Accepted for publication Nov 17, 1988.

From the Division of Pediatric Cardiology, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore.

Reprint requests to Division of Pediatric Cardiology, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205 (Dr Zahka).

METHODS

The BWIS is a population-based study of infants in whom diagnoses of cardiovascular malformations at less than 1 year of age were confirmed by echocardiography, cardiac catheterization, surgery, or autopsy.[4,5] The protocol and questionnaires used have been approved by the appropriate institutional review boards. The study area includes the state of Maryland, the District of Columbia, and six counties in Northern Virginia. Patients are entered into the study by the pediatric cardiology clinics in the area. Completeness of ascertainment is assured by a community search of birth and autopsy records.[6] Premature infants with isolated patent ductus arteriosus (PDA) are excluded from the study. Chromosomal abnormalities were found in 12.5% of infants with cardiac malformations and 0.1% of controls.[5] Congenital heart defects were coded using the system developed by the International Society of Cardiology.[4,7]

Between January 1981 and December 1986, 166 infants with DS were registered in the BWIS and had one-year follow-up information available. Of these, 160 (96%) had one of the following defects: (1) complete atrioventricular canal (CAVC), (2) partial atrioventricular canal (PAVC), (3) ventricular septal defect (VSD), (4) secundum atrial septal defect (ASD), (5) tetralogy of Fallot (TOF), or (6) PDA. The remaining six infants with DS were excluded from the study group.

For comparison of the referral and clinical care patterns, we studied the records of the 540 infants enrolled in the BWIS over the same time period who had the same cardiac diagnoses but no chromosomal or other extracardiac anomalies. This comparison group had ICMs.

A CAVC was defined as an ostium primum type of ASD together with a nonrestrictive VSD of the endocardial cushion or atrioventricular canal type. A PAVC included an ostium primum ASD with or without additional restrictive defects in the ventricular septum and isolated endocardial cushion VSDs.

A VSD included defects in the perimembranous or muscular ventricular septum regardless of their size or hemodynamic impact. An ASD included only ASDs of the ostium secundum type. Patent ductus arteriosus was the only cardiac defect in the PDA group.

The records of the infants with DS and ICMs in these six diagnostic groups were analyzed for the age at diagnosis, history of surgical intervention, and mortality by one-year follow-up. The association of age at the time of diagnosis, anatomical diagnosis, age at surgery, and medical and surgical mortality with DS vs ICM was evaluated using the χ^2 test. All statistical analyses were performed using the SAS system.[8]

RESULTS

The relative distribution of defects differed markedly among the six diagnostic groups. In the DS group, CAVC or PAVC defects predominated (102/160 infants [64%]). Among infants with ICM, VSDs were the most frequent (314/540 infants [58%]). The proportions of infants with ASDs, PDA, and TOF were similar in the two groups (Table 1).

The age at cardiac diagnosis is shown in the Figure. By age 13 weeks, 78% of infants with DS and 67% of infants with ICM had been referred and had their cardiac diagnosis confirmed ($P<.01$). By age 26 weeks the proportion of infants with a diagnosis in both groups was comparable. The diagnoses PAVC and ASD were recognized earlier in the infants with DS.

Surgery was performed before 1 year of age in 62% (99/160) of infants in the DS group and in 26% (141/540) of the infants with ICMs. Surgical procedures are presented by individual defect in Table 2. The proportion of infants with DS who underwent cardiac surgery in infancy was higher among those with

Table 1.—Cardiovascular Diagnoses in Infants With DS and ICM*

Group	No. of Infants	Diagnosis, No. (%) of Infants					
		CAVC	PAVC	VSD	ASD	TOF	PDA
DS	160	82 (51)	20 (13)	26 (16)	16 (10)	10 (6)	6 (4)
ICM	540	10 (2)	22 (4)	314 (58)	84 (16)	80 (15)	30 (6)

*DS indicates Down syndrome; ICM, isolated cardiovascular malformation; CAVC, complete atrioventricular canal; PAVC, partial atrioventricular canal; VSD, ventricular septal defect; ASD, atrial septal defect; TOF, tetralogy of Fallot; and PDA, patent ductus arteriosus.

Table 2.—Diagnosis-Specific Comparison of Surgery by 1 Year of Age in Infants With DS and ICM*

Group	No. (%) of Infants by Diagnosis					
	CAVC	PAVC	VSD	ASD	TOF	PDA
Infants Who Underwent Surgery by 1 y of Age						
DS	66/82 (80)	8/20 (40)	14/26 (54)	1/16 (6)	6/10 (60)	4/6 (67)
ICM	4/10 (40)	10/22 (45)	49/314 (16)	7/84 (8)	60/80 (63)	21/30 (70)
P	<.005	NS	<.001	NS	NS	NS
Mortality by 1 y in Surgically Treated Infants						
DS	19/66 (29)	0/8	0/14	0/1	0/6	0/4
ICM	3/4 (75)	2/10 (20)	5/49 (10)	0/7	11/60 (18)	0/21
P	NS	NS	NS	NS	NS	NS

*DS indicates Down syndrome; ICM, isolated cardiovascular malformation; CAVC, complete atrioventricular canal; PAVC, partial atrioventricular canal; VSD, ventricular septal defect; TOF, tetralogy of Fallot; PDA, patent ductus arteriosus; and NS, not significant.

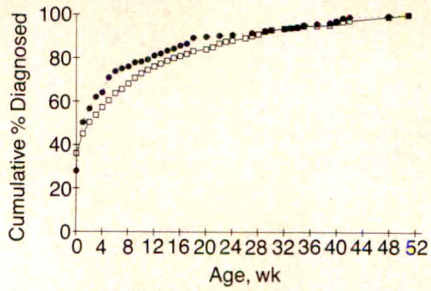
Table 3.—Mortality by 1 Year of Age in Medically Treated Infants With DS and ICM*

Group	Mortality by Diagnosis, No. (%) of Infants					
	CAVC	PAVC	VSD	ASD	TOF	PDA
DS	9/16 (56)	0/12	1/12 (8)	1/15 (7)	0/4	0/2
ICM	4/6 (67)	3/12 (25)	1/265 (0.4)	1/77 (1)	3/30 (10)	0/9
P	NS	NS	<.005	NS	NS	NS

*DS indicates Down syndrome; ICM, isolated cardiovascular malformation; CAVC, complete atrioventricular canal; PAVC, partial atrioventricular canal; VSD, ventricular septal defect; ASD, secundum atrial septal defect; TOF, tetralogy of Fallot; PDA, patent ductus arteriosus; and NS, not significant.

CAVCs and VSDs. The surgery rates for ASDs, TOF, and PDA were similar in the DS and ICM groups. Among infants who underwent surgery, the overall mortality rate by 1 year of age was 19% (19/99) in infants with DS and 15% (21/141) in infants with ICM (Table 2). There was no significant difference in surgical outcome in the diagnostic subgroups.

A total of 460 infants did not undergo cardiac surgery before 1 year of age, and 437 (95%) were alive at their one-year follow-up (Table 3). The medical mortality rate by 1 year of age was 18% (11/61) in the DS group vs 3% (12/399) in the ICM group ($P<.001$). Nine of the 11 deaths in the DS group and seven of the 12 deaths in the ICM group were among infants with CAVCs or PAVCs, indicating that the higher overall one-year mortality rate among the infants with DS was due to the severity of their cardiac defects. The ICM group contains a much greater proportion of infants with small VSDs that did not require surgery in the first year of life. One hundred twenty-six (79%) of the 160 infants with DS had "severe" cardiac defects (CAVC, PAVC, TOF, or large VSD that required surgery in infancy) compared with only 161 infants (30%) in the ICM group. The mortality rate at 1 year of age among infants with "severe" defects was 22.8% in the DS group and 25.5% in the ICM group.



Cumulative percentage of infants in Down syndrome (solid circles) and isolated cardiovascular malformation (open squares) groups diagnosed by end of each week over first year of life. Earlier diagnosis is demonstrated in infants with Down syndrome during first 13 weeks, but groups are comparable by week 26.

COMMENT

Sondheimer et al[3] suggested that infants with DS receive unequal cardiac care due either to delay in referral for cardiac evaluation or to failure to proceed with timely surgical treatment of recognized defects. Their study was limited to patients with CAVCs confirmed at cardiac catheterization between 1977 and 1982. They concluded that delayed initial referral was the major impediment to cardiac care. The goal of our study was to define the contemporary patterns of care for children with DS and a broad spectrum of heart defects in the BWIS area. We speculated that previous differences in the cardiac care of infants with DS would no longer be observed. Our study includes the use of all currently available diagnostic tools and reflects increased awareness of the benefits of early surgical repair of congenital heart disease.[9]

In the BWIS, virtually complete ascertainment of infants with a diagnosis of congenital heart disease by 1 year of age is assured by careful reporting by all the pediatric cardiac centers as well as review of regional pathology lists and death certificates.[4,6] The study identifies only those infants born with DS in the region who have heart defects. Our data indicate that over the first year of life the patterns of referral for DS and ICM are similar. While it is possible that some infants with DS or ICMs born during the study period may have escaped

ascertainment, the large proportion of infants assigned a diagnosis before 6 months of age suggests that, in fact, diagnosis is not delayed in either group.

For four defects (PAVC, ASD, TOF, and PDA) there was no significant difference in the frequency of surgery in the first year. The increased prevalence of surgery in infants with DS and CAVCs or VSDs in the first year of life is likely due to larger defects, more symptoms, or the recognized risk of pulmonary vascular disease at an early age in DS; these factors may also contribute to increased perioperative risk in older children with DS.[10] These data indicate that there is no physician or parental bias about the suitability of surgery for infants with DS.[11]

Infants with DS born in the BWIS area receive comparable cardiac care as determined by the age at diagnosis, the timing of surgery, and the performance of cardiac surgery for defects of comparable severity. Timely referral of infants with DS, including those without cardiac murmurs, probably is the result of increased awareness among pediatricians of the prevalence of heart disease in infants with DS and of the benefits of early cardiac repair.

This study was supported by grant HL-25629 from the National Heart, Lung, and Blood Institute.

The following Baltimore-Washington Infant Study coinvestigators supported this research: Charlotte Ferencz, MD, MPH, Joann A. Boughman, PhD, Joel I. Brenner, MD, John W. Downing, MD, MPH, Seymour I. Hepner, MD, Robert J. McCarter, ScD, Judith D. Rubin, MD, and Lowell W. Perry, MD.

We thank Kim Hofmeister for assistance in data analysis.

References

1. Park SC, Mathews RA, Zuberbuhler JR, et al: Down syndrome with congenital heart malformations. *AJDC* 1977;131:29-33.

2. Katlic MR, Clark EB, Neill CA, et al: Surgical management of congenital heart disease in Down's syndrome. *J Thorac Cardiovasc Surg* 1977;74:204-209.

3. Sondheimer HM, Byrum CJ, Blackman MS: Unequal care for children with Down's syndrome. *AJDC* 1985;139:68-70.

4. Ferencz C, Rubin JD, McCarter RJ, et al: Congenital heart disease: Prevalence at live birth: The Baltimore-Washington Infant Study. *Am J Epidemiol* 1985;121:31-36.

5. Ferencz C, Rubin JD, McCarter RJ, et al: Cardiac and noncardiac malformations: Observations in a population-based study. *Teratology* 1987;35:367-378.

6. Rubin JD, Ferencz C, Brenner JI, et al: Early detection of congenital cardiovascular malformations in infancy. *AJDC* 1987;141:1218-1220.

7. International Society of Cardiology: *Classification of Heart Disease in Childhood.* Groningen, Netherelands, VRB Offsetdrukkerij, 1970.

8. *SAS User's Guide: Basics, Version 5 Edition.* Cary, NC, SAS Institute Inc, 1985.

9. Santos A, Boucek M, Ruttenberg H, et al: Repair of atrioventricular septal defects in infancy. *J Thorac Cardiovasc Surg* 1986;91:505-510.

10. Morray JP, MacGillivray R, Duker G: Increased perioperative risk following repair of congenital heart disease in Down's syndrome. *Anesthesiology* 1986;65:221-224.

11. Bull C, Rigby ML, Shinebourne EA: Should management of complete atrioventricular canal defect be influenced by coexistent Down syndrome? *Lancet* 1985;1:1147-1149.

In Other AMA Journals

JAMA

Recall and Eye Tracking Study of Adolescents Viewing Tobacco Advertisements

P. M. Fischer; J. W. Richards, Jr; E. J. Berman; D. M. Krugman (*JAMA*. 1989;261:90)

Subhypothalamic High-Intensity Signals Identified by Magnetic Resonance Imaging in Children With Idiopathic Anterior Hypopituitarism

Evidence Suggestive of an 'Ectopic' Posterior Pituitary Gland

Allen W. Root, MD; Carlos R. Martinez, MD; Lawrence R. Muroff, MD

• Magnetic resonance imaging in two children with idiopathic hypopituitarism demonstrated a signal of high intensity near the optic tract that was consistent with the signal produced by posterior pituitary tissue. Patient 1 was a 15-year-old girl with panhypopituitarism but intact posterior pituitary function. Computed tomography disclosed widening of the superior aspect of the pituitary stalk and a partially empty sella. Magnetic resonance imaging disclosed a 3-mm high-intensity signal abutting the optic tract in the midline just above the sella. The pituitary stalk was not clearly defined, the pituitary gland was small, and the sella was filled with cerebrospinal fluid. Patient 2 was a 12-year-old boy with isolated deficiency of growth hormone secretion. Findings from magnetic resonance imaging and computed tomography were similar to those in patient 1. These data suggest that the high-intensity magnetic resonance imaging findings represent a displaced or "ectopic" posterior pituitary gland, and that the hypopituitary state is due to an insult to the pituitary stalk.

(*AJDC*. 1989;143:366-367)

Magnetic resonance imaging (MRI) and computed tomography (CT) have delineated the in vivo structure of the hypothalamus and anterior and posterior pituitary gland in normal subjects and in patients with clinical disorders of this axis.[1,2] Computed tomography has disclosed a high incidence of empty sella and small sellar volume in patients with idiopathic hypopituitarism.[2,3] By MRI (T_1-weighted images) the posterior pituitary emits a signal of high intensity attributed to the intracellular cytoplasmic lipid of pituicytes that is believed to reflect the synthesis and secretion of antidiuretic hormone (Figure, top left).[1,4,5] This signal is absent in patients with diabetes insipidus (Figure, top right). Fujisawa et al[6] initially reported the absence of the characteristic posterior pituitary signal in 10 patients with idiopathic anterior hypopituitarism and the presence of a high intensity signal in 7 of 10 subjects at the base of the hypothalamus near or at the proximal stump of the pituitary stalk. They suggested that this signal represented a displaced or "ectopic" posterior pituitary gland, the consequence of an insult to the pituitary stalk as a result of birth trauma. These investigators[7] subsequently characterized pituitary function in the hyposomatotropic subjects with pituitary stalk transection, and found subnormal to normal thyrotropin and gonadotropin secretion related to the size of the residual gland. They speculated that the hypothalamic-pituitary portal vasculature was partially reestablished in some patients.

Herein we describe two children with idiopathic anterior hypopituitarism and MRI findings similar to those described by Fujisawa et al.[6]

Accepted for publication December 20, 1988.

From the Departments of Pediatrics and Radiology, University of South Florida College of Medicine, Tampa, and the All Children's Hospital, St Petersburg, Fla.

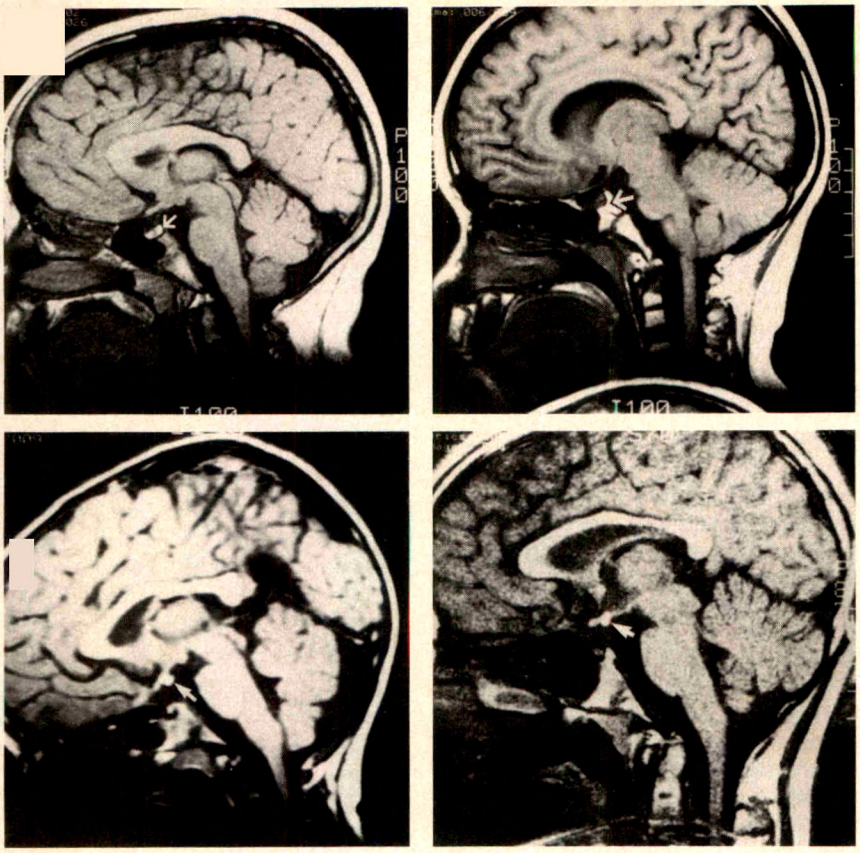
Presented at the American Pediatric Society/Society for Pediatric Research, Washington, DC, May 3, 1988.

Reprint requests to All Children's Hospital, 801 6th St South, St Petersburg, FL 33731 (Dr Root).

PATIENT REPORTS

PATIENT 1.—This patient was a 15-year-old girl in whom the diagnosis of hypopituitarism was established at 22 months of age after presentation with recurrent hypoglycemic seizures and growth retardation (height age, 10 months). She was the product of a pregnancy complicated by vaginal spotting in the first trimester, and she was born by spontaneous vaginal, vertex delivery; her birth weight was 2.2 kg. On the second day of life a seizure occurred, after which the blood glucose concentration was 3.3 mmol/L. Over the next 2 years this infant had multiple seizures and was treated with anticonvulsant medications. Hypoglycemia (glucose level, 0.3 mmol/L) was first documented at 15 months of age. Patient 1 had panhypopituitarism (documented deficiencies of growth hormone [growth hormone peak level, 1.7 μg/L after hypoglycemia, <1.0 μg/L after levodopa], thyrotropin [thyroxine level, 33 nmol/L], and luteinizing hormone [luteinizing hormone level, <1.0 IU/L after growth hormone releasing hormone administration]), but did have intact posterior pituitary function (urinary specific gravity, 1.031). A CT scan demonstrated widening of the superior aspect of the pituitary stalk and a partially empty sella turcica. T_1-weighted MRI disclosed a 3-mm high-intensity signal inferior to the optic tract in the midline (Figure, bottom left).

PATIENT 2.—At 8 years of age this patient presented with short stature (height age, 4.5 years). He was the product of a pregnancy complicated by maternal bronchiectasis. He was delivered vaginally in the vertex position at 36.5 weeks' gestation with a birth weight of 2.4 kg. The neonatal period was complicated by respiratory distress, hypotonia, and weight loss, which all resolved by 8 days of age. There was no significant growth hormone secretory response to insulin hypoglycemia (growth hormone peak level, 3.9 μg/L), clonidine (growth hormone peak level, 3.6 μg/L), or levodopa (growth hormone peak level, 3.7 μg/L), but after administration of growth hormone releasing hormone a peak growth hormone value of 16.6 μg/L was



Sagittal magnetic resonance image (T_1-weighted images) of the central nervous system. Top left, Normal subject with high-intensity signal emanating from the posterior pituitary within the pituitary fossa (arrow). Top right, Absence of intrasellar high-intensity signal in an 8-year-old boy with central diabetes insipidus. Bottom left and right (patients 1 and 2, respectively), Note high-intensity signal inferior to the optic chiasm in both patients (arrows).

recorded. The thyrotropin secretory response to thyrotropin-releasing hormone was delayed and prolonged (peak thyrotropin level, 10.0 mU/L 120 minutes after thyrotropin-releasing hormone administration). Patient 2 entered puberty spontaneously; gonadotropin secretion after administration of gonadotropin-releasing hormone was low-normal for a pubertal subject (peak luteinizing hormone level, 12 IU/L after gonadotropin-releasing hormone administration). The CT and MRI findings were similar to those of patient 1 (Figure, bottom right).

COMMENT

The posterior pituitary is composed of axon terminals whose cell bodies are in the supraoptic and paraventricular nuclei. These axons contain antidiuretic hormone, oxytocin, and their carrier neurophysins and are surrounded by cells termed *pituicytes*. Computed tomography has demonstrated a high incidence of morphologic abnormalities of the pituitary stalk and gland in patients with idiopathic hypopituitarism, including aplasia and hypoplasia of the pituitary gland, absence or hypoplasia of the pituitary stalk, and small sellar volumes.[2,3,8] Stanhope et al[2] also identified by high-resolution CT a spheroidal structure at the base of the hypothalamus that they suggested might be a neurohypophysis. Magnetic resonance imaging has confirmed these findings and has identified subhypothalamic tissue with a signal of high intensity, in all likelihood the residual neurohypophysis, that perhaps was stimulated to grow and function as a result of transection of the pituitary stalk due to perinatal trauma.[4,6] In experimental animals ligation or transection of the pituitary stalk is followed by the formation of a functional posterior pituitary proximal to the insult.[6] In addition to our patients and those of Fujisawa et al,[6] Kelly et al,[4] Pellini et al,[9] and Werder et al[10] have reported similar MRI findings in 21 additional patients with idiopathic hypopituitarism, indicating that the displaced or "ectopic" posterior pituitary may be common in this disorder.

We thank Etta Tucker for helpful secretarial assistance.

References

1. Fujisawa I, Asato R, Nishimura K, et al. Anterior and posterior lobes of the pituitary gland. assessment by 1.5T MR imaging. *J Comp Asst Tomogr*. 1987;11:214-220.

2. Stanhope R, Hindmarsh P, Kendall B, Brook CGD. High resolution CT scanning of the pituitary gland in growth disorders. *Acta Paediatr Scand*. 1986;75:779-786.

3. Smith, SP, Wolpert SM, Sadeghi-Nejad A, Senior B. Value of computed tomographic scanning in patients with growth hormone deficiency. *Pediatrics*. 1986;78:601-605.

4. Kelly WM, Kucharczyk W, Kucharczyk J, et al. Posterior pituitary ectopia: an MR feature of pituitary dwarfism. *AJNR*. 1988;9:453-460.

5. Kucharczyk J, Kucharczyk W, Berry I, et al. Histochemical characterization and functional significance of the hyperintense signal on MR images of the posterior pituitary. *AJNR*. 1988;9:1079-1083.

6. Fujisawa I, Kikuchi K, Nishimura K, et al. Transection of the pituitary stalk: development of an ectopic posterior lobe assessed with MR imaging. *Radiology*. 1987;165:487-489.

7. Kikuchi K, Fujisawa I, Momoi T, et al. Hypothalamic pituitary function in growth hormone-deficient patients with pituitary stalk section. *J Clin Endocrinol Metab*. 1988;67:817-823.

8. Pococco M, De Campo C, Marinoni S, et al. High incidence of primary empty sella syndrome in children with growth hormone deficiency. In: Program and abstracts of European Society for Pediatric Endocrinology; June 26-29, 1988; Copenhagen, Denmark. Abstract 72.

9. Pellini C, di Natale B, Petecca C, et al. MR imaging of pituitary gland and stalk in idiopathic growth hormone deficiency. In: Program and abstracts of European Society for Pediatric Endocrinology; June 26-29, 1988; Copenhagen, Denmark. Abstract 73.

10. Werder EA, Zachmann M, Wichmann W, et al. Growth hormone insufficiency associated with a small nodule of the pituitary stalk: neurohypophyseal ectopy? In: Program and abstracts of European Society for Pediatric Endocrinology; June 26-29, 1988; Copenhagen, Denmark. Abstract 74.

Effects of Theophylline on Behavior and Learning in Children With Asthma

Leonard Rappaport, MD; Hugh Coffman, PhD; Richard Guare, PhD;
Terrance Fenton, EdD; Christopher DeGraw, MD; Francis Twarog, MD, PhD

• This study examined the potential side effects of theophylline on behavior, attention, memory, and fine motor function in children with asthma. Seventeen children of normal intelligence who were intermittent theophylline users were recruited. Each was not taking medication at the initiation of the study. During the study, each child took the study medication (Theo-Dur tablets, 14 to 16 mg/kg per day or their usual dose, whichever was higher, or placebo) divided every 12 hours for 3½ days (seven doses). A double-blind crossover design was employed such that each subject was randomly assigned to a group receiving theophylline/placebo or placebo/theophylline. After the first period, subjects were tested on a neuropsychological battery designed to assess cognitive performance, while the children, parents, and teachers filled out questionnaires concerning behavior and attention. The same procedure was repeated two weeks later (period 2) under the opposite drug condition. Data were analyzed by means of an analysis of variance, with time (period 1 vs period 2 [performance]) as a repeated measure and medication group as a between-subjects factor. Dependent variables consisted of 27 measures of performance, behavior, and attention. Only one of the 27 analyses revealed a significant group by time interaction. This analysis suggested a significant improvement in memory while taking theophylline; however, a different form of the same test showed no effect. Children and parents also completed a side-effects scale under both drug conditions. When the children were taking theophylline, parents and children noted that the children had more stomachaches and children noted more "shaking hands." The following observations suggest that the failure to find significant behavioral side effects while taking theophylline is not due to the relatively small sample size: (1) Almost all of the analyses fell far short of statistical significance, with findings indicating no trends toward poor performance while taking medication. (2) Correlations between the theophylline level and change in performance clustered around zero, with positive and negative values occurring with about equal frequency. (3) Neither parents nor children could accurately guess the child's medication condition. Thus, although there have been numerous reports on the behavioral side effects of theophylline, such reactions were not revealed in this study.

(*AJDC* 1989;143:368-372)

Asthma is a common disease of childhood that occurs in approximately 5% of all children.[1] In the United States, a theophylline preparation has been generally considered the drug of choice when pharmacologic treatment is necessary.[2] This study was performed to evaluate the possible behavioral and cognitive side effects of theophylline in children with asthma.

In the past several years, there have been increasing numbers of clinical reports of negative behavioral and cognitive side effects of theophylline preparations. These side effects have included hyperactivity, decreased attention span, jitteriness, and insomnia. The hypothesis that theophylline, at some serum level, will have central nervous system side effects is consistent with the known pharmacologic properties of methylxanthine compounds.[3] Caffeine, another methylxanthine, has been studied extensively and has been shown to improve alertness and attention at low levels in adults while inducing insomnia and tremors at higher levels.[4] The theoretical prediction that theophylline could have behavioral and cognitive side effects, in combination with anecdotal reports of such effects, has convinced a number of clinicians to employ other asthma medications in place of theophylline.

A number of recent studies have shown changes in behavior and learning in children while taking theophylline.[5-9] These studies, however, have all exhibited methodological weaknesses that have tended to raise concerns about the findings. Most of the studies have been unblinded and have often involved children whose parents felt, prior to the study, that their children exhibited negative side effects from theophylline preparations, therefore introducing a bias toward finding ill effects. Moreover, these studies have been done on children with active asthma and have failed to differentiate the behavioral side effects of the disease from those of the medication. One exception was a recent random double-blind parallel study by Rachelefsky et al[7] on nonselected well children with asthma. Rachelefsky et al did find evidence of negative side effects of theophylline on attention and activity as noted by teacher questionnaires, but no other areas of deterioration were seen either by parent observation or by psychological testing. A study by Joad et al,[10] on the other hand, followed up 18 adults and adolescents in a three-way blinded crossover between theophylline, albuterol, and placebo and found improved sustained attention while taking the-

Accepted for publication Nov 9, 1988.

From the Division of Ambulatory Pediatrics (Drs Rappaport, DeGraw,and Fenton), Division of Allergy (Dr Twarog) and Department of Psychiatry (Drs Coffman and Guare), The Children's Hospital, and the Department of Pediatrics, Harvard Medical School (Drs Rappaport, DeGraw, and Twarog), Boston.

Read in part at the annual meeting of The Society for Behavioral Pediatrics, Washington, DC, May 1986.

Reprint requests to The Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (Dr Rappaport).

ophylline, with negative side effects similar to those found with caffeine.

The present investigation was designed to explore theophylline's effects on behavior, as assessed by teacher and parent questionnaires in addition to psychological tests. The study used a double-blind crossover design to test for these effects on children with asthma who did not have active symptoms at the time of the study.

PATIENTS AND METHODS

Seventeen children with asthma who were between the ages of 6 and 12 years were recruited from a referral allergy practice and a primary care pediatric practice. All children (11 boys, six girls) had a history of intermittent theophylline treatment for asthma but were not receiving medication at the time the study was initiated. None of the children had developmental problems. The population was predominantly middle and upper-middle class.

The study employed a double-blind crossover design such that subjects were randomly assigned to one of two conditions. One group was administered theophylline during an initial 3½-day period and a placebo during a second 3½-day period two weeks later (N = 9). A second group, treated under the opposite conditions, received the placebo during the first period and theophylline during the second (N = 8). Neither the patients nor the testers were informed whether placebo or theophylline was being administered. The medication employed was Theo-Dur tablets,14 to 16 mg/kg per day, or the child's usual dose, whichever was higher, divided every 12 hours for 3½ days or seven doses (Wednesday morning through Saturday morning). The medication and placebo looked identical. None of the subjects were taking any other medications during the study period. While each child was taking the study medication or the placebo, parents and teachers filled out a number of questionnaires describing the child's behavior and attention. Parents were asked to complete the Connors' Abbreviated Questionnaire,[11] the ANSER System Activity/Attention Scale,[12] and a side-effects scale that included ratings of headaches, stomachaches, nervousness, insomnia, chest pain, irritability, and rashes. Teachers were asked to complete the Connors' Abbreviated Questionnaire[11] and the ANSER Activity/Attention Scale.[12] Each child completed a side-effects scale and the Children's Manifest Anxiety Scale,[13] a scale designed to assess anxiety state (Table 1). At the end of the medication period, each child was tested using a battery of neuropsychological tests designed to assess various aspects of cognitive and fine motor performance. Neuropsychological tests administered included the Kløve Pegs (Kløve Peg Board, Lafayette Instrument Co, Lafayette, Ind, 1977), Logical Memory Passages (Forms A and B),[14] the Wechsler Intelligence Scale for Children-Revised (WISC-R)[15] WISC-R Digit Span, WISC-R Coding, the Matching Familiar Figures Test,[16] an auditory, continuous-performance test, and the Porteus Mazes[17] (Table 2). The same procedure was repeated two weeks later on the opposite study drug. The two-week period was chosen to allow sufficient washout from theophylline preparations.

Table 1.—Questionnaires Administered

Parent
Connors' Abbreviated Questionnaire
ANSER System—Activity/Attention Questionnaire
Side-effects Questionnaire
Teacher
Connors' Abbreviated Questionnaire
ANSER System—Activity/Attention Questionnaire
Child
Children's Manifest Anxiety Scale
Side-effects scale

Table 2.—Neuropsychological Tests

Test	Area Assessed
Kløve Pegs	Fine motor speed and dexterity
Logical Memory Passages (A and B)	Short-term verbal memory/ attention
WISC-R* Digit Span	Repetition/ attention
WISC-R Coding	Fine motor/ attention and learning
Matching Familiar Figures	Attention/ impulsivity
Auditory Continuous Performance Test	Sustained auditory attention
Porteus Mazes	Impulsivity-learning

*WISC-R indicates Wechsler Intelligence Scale for Children, revised.

All questionnaires and neuropsychological tests were chosen to examine performance in areas thought to be particularly susceptible to the proposed side effects of theophylline. These areas included attention, activity, fine motor control, and general behavior.

The 3½-day study period was chosen because the induction stage of theophylline therapy has been shown in previous reports to have the highest incidence of side effects.[18-20] If behavioral and cognitive deficits were associated with theophylline therapy, it seemed most likely that these decrements would be evident in this induction stage.

At the beginning of each Saturday testing session, both the child and the parent were asked to judge whether the child was, at the time, receiving placebo or medication. At the end of the testing session, 15 of the 17 subjects had theophylline levels measured approximately three hours after the fifth dose of theophylline. Two children, who were twins, refused blood drawing on the day of testing.

This protocol was approved by the Committee on Clinical Investigation at The Children's Hospital, Boston. Informed consent was obtained from all participating parents and children.

RESULTS

Data were analyzed by means of an analysis of variance[21] with *time* (period 1 vs period 2 performance) as a repeated measure and *medication group* as a between-subjects factor. Dependent variables consisted of the 20 measures of performance, behavior, and attention as taken from the questionnaires and neuropsychological tests previously described. If theophylline were interfering with cognitive and behavioral functioning, it would be expected that performance on many of these measures would be significantly depressed while taking theophylline relative to performance while taking placebo. The appropriate statistical test for such an effect in a crossover design is the Medication group by time interaction; this provides a test of whether group performance changed significantly from one testing period to the next as a function of the reversal in medication.

Table 3 shows the results of the analyses for the data obtained from the questionnaires administered to the parents, teachers, and children. The direction of change from placebo to medication condition and vice versa varied, showing neither a pattern of improvement nor deterioration as the drug condition was reversed. While theophylline was being taken, the trend was for parents to see slight worsening and for teachers to see improvement in behavior, but these changes were not statistically significant.

The side-effects scales were analyzed by a Sign Test and did reveal changes while theophylline was being taken. Parents reported more stomachaches during the medication period ($P<.05$), and there were trends toward more headaches ($P=.09$) and nervousness

Table 3.—Mean Questionnaire Scores*			
	Placebo	Theophylline	P
Parent ANSER Questionnaire (↑ = better)			
Group 1	1.61	1.50	.35
Group 2	1.61	1.47	
Parent Connors' Questionnaire (↑ = worse)			
Group 1	4.88	7.25	.32
Group 2	4.88	5.44	
Teacher ANSER Questionnaire (↑ = better)			
Group 1	1.64	1.74	.15
Group 2	1.77	1.80	
Teacher Connors' Questionnaire (↑ = worse)			
Group 1	4.38	4.37	.20
Group 2	5.11	3.44	
Children's Manifest Anxiety Scale			
Group 1	14.50	13.66	.28
Group 2	6.42	10.10	

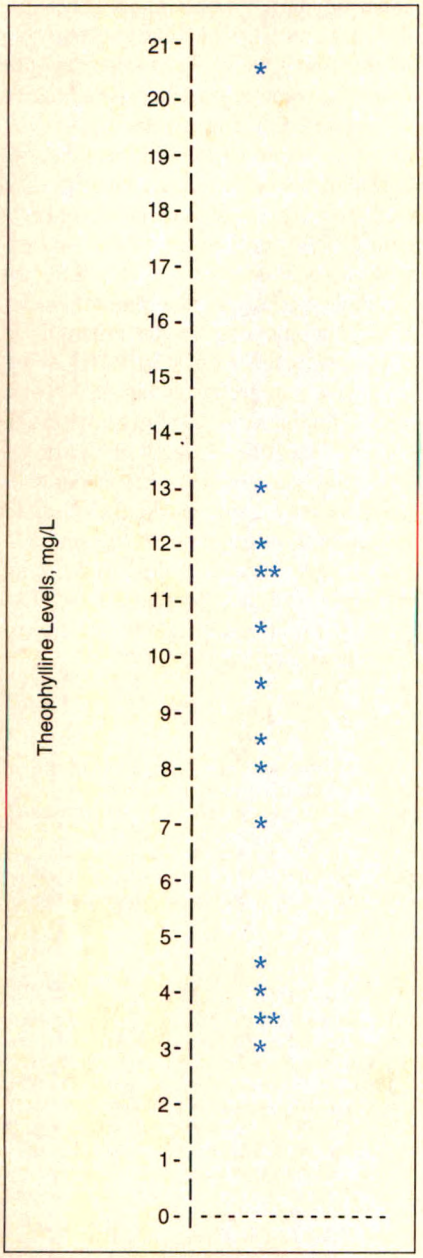
*Group 1 indicates placebo/theophylline; group 2, theophylline/placebo.

($P = .09$). While taking theophylline, children reported more stomachaches ($P < .05$) and "shaking hands" ($P < .05$) and a trend toward more headaches ($P = .055$).

Neuropsychological tests as outlined in Table 4 failed to show significant and interpretable changes while the subjects were taking theophylline. The Logical Memory Test, Form B, showed improvement when taking theophylline ($P < .05$) while an alternative form of the same test, Form A, showed no trend in either direction. Although there were trends in a few of the remaining tests, they were equally divided between improvement and deterioration while taking theophylline, with none ap-

Table 4.—Mean Neuropsychological Test Scores*							
	Placebo	Theophylline	P	Test	Placebo	Theophylline	P
Kløve Pegs Trial 1				Digit Span overall scaled score			
Group 1 (Time)	64.12	63.62	.58	Group 1	11.12	11.62	.29
Group 2	71.88	75.33		Group 2	9.44	10.11	
Kløve Pegs Trial 2				Digit Span overall—raw score			
Group 1	60.25	60.00	.65	Group 1	9.00	12.00	.21
Group 2	72.00	70.44		Group 2	9.71	10.85	
Kløve Pegs Trial 1 Nondominant Hand				Coding—raw score			
Group 1	79.50	71.12	.71	Group 1	47.62	51.00	.59
Group 2	85.44	90.67		Group 2	43.62	41.75	
Kløve Pegs Trial 2 Nondominant Hand				Coding—standard score			
Group 1	70.25	68.12	.45	Group 1	12.62	13.37	.72
Group 2	84.77	82.11		Group 2	11.62	11.11	
Logical Memory A				Matching familiar figures (mean latency)			
Group 1	9.00	9.62	.61	Group 1	15.88	13.05	.62
Group 2	9.92	8.55		Group 2	11.56	13.42	
Logical Memory B				Matching familiar figures			
Group 1	9.68	10.81	.04	Group 1	7.00	7.75	.53
Group 2	9.72	11.16		Group 2	7.66	8.22	
Digit Score (scaled score)				Auditory CPT A omissions			
Group 1	6.37	7.25	.51	Group 1	2.25	0.62	.49
Group 2	5.77	5.44		Group 2	1.77	2.44	
Digit Score (absolute score)				Auditory CPT A commissions			
Group 1	5.75	6.37	.43	Group 1	1.50	0.62	.80
Group 2	5.44	5.22		Group 2	0.33	1.33	
Backwards Digit (scaled score)				Auditory CPT X omissions			
Group 1	5.25	5.00	.10	Group 1	1.50	1.00	.96
Group 2	4.77	4.22		Group 2	2.00	2.55	
				Auditory CPT X commissions			
				Group 1	0.87	0.25	.91
				Group 2	0.22	0.77	
Backwards Digit (absolute score)				Porteus Mazes—unsuccessful trials			
Group 1	4.12	3.75	.06	Group 1	6.12	5.25	.12
Group 2	3.88	3.44		Group 2	6.55	10.00	
				Porteus Mazes—test age			
				Group 1	13.37	14.37	.48
				Group 2	13.05	11.27	

*Group 1 indicates placebo/theophylline; group 2, theophylline/placebo; CPT, continuous performance test.



Subjects' theophylline levels.

proaching statistical significance.

Theophylline levels in the sample ranged from 3.2 mg/L to 20.6 mg/L (Figure). All levels were measured approximately three hours after the fifth dose of medication. The mean theophylline level was 8.9 mg/L. To evaluate the effects of the varying theophylline levels, change of performance from taking placebo to taking theophylline was correlated with the serum theophylline levels using a Spearman *r* rank order correlation. Variables chosen for this analysis were those that showed deterioration while receiving theophylline, and those in which *P* values in the original analyses most nearly approached statistical significance. Table 5 shows that the correlations between these variables and theophylline levels clustered around 0, with both positive and negative correlations occurring.

Table 5.—Test/Questionnaire Change Scores vs Theophylline Levels

Test	Spearman *r*	*P*
Reverse Digit Span	.08	.78
Logical Memory Passages	−.20	.48
Parent Questionnaire	−.17	.55
Connors'-Parent Questionnaire	.18	.52
Children's Manifest Anxiety Scale	.20	.52
Connors'-Teacher Questionnaire	.01	.97

Parents and children were both asked at the beginning of each test session whether they felt medication or placebo was being taken. Neither parents nor children could accurately guess the child's medication status, although their guesses were somewhat more accurate in the second testing session than in the first.

COMMENT

This study found remarkably few side effects of theophylline on attention, activity, or behavior as assessed by parent or teacher questionnaires. Moreover, neuropsychological tests, designed to assess fine motor control, attention, impulsivity, and memory, failed to reveal any consistent side effects of this medication. Changes were limited to one test of memory that showed improvement while taking theophylline. This single change in performance could easily have occurred by chance in light of the many tests of significance and the fact that no change in performance was seen on an alternative form of the same test. In addition, positive effects of theophylline appeared to be randomly interspersed with negative effects across the battery of tests and questionnaires. Thus, this study failed to find support for the hypothesis that theophylline causes decremental changes in behavior, attention, and school performance, at least in the initial induction stage of therapy.

Some methodological and design factors may explain the differences in findings between this study and others in the literature that report negative side effects.[5-10] First, the children in this study did not have active asthma during the study protocol. Therefore, effects of the asthma itself could not complicate interpretation of theophylline's adverse side effects. Second, the double-blind crossover design of this study eliminates biased comparisons of unequivalent small groups and minimizes the effects of parental bias concerning theophylline.

It seems particularly necessary to comment on possible explanations for the differences between the negative conclusions of this study and the positive conclusions, with a similar population, in the study by Rachelefsky et al.[7] Many of the findings of the two studies were in fact identical. Both studies showed no change on similar parent questionnaires and psychological tests designed to assess attention, memory, fine motor control, and impulsivity. The one area where Rachelefsky et al did show a negative change while theophylline was being taken was on the teacher questionnaires, especially in the area of aggressivity and difficulty in completion of work. Our study, on the other hand, which used similar teacher questionnaires, showed a trend, although not a significant one, toward improvement while taking theophylline. One explanation for this difference could be the presence of confounding factors, such as the repeated blood drawing in the Rachelefsky et al theophylline group, which itself might cause deterioration in behavior. Another explanation could be that the short-term nature of our study did not yield the same decrements in behavior as did the longer-term study by Rachelefsky et al. Finally, it is possible that our lower serum theophylline level might improve behavior while the higher levels in the study by Rachelefsky et al (range 10 to 20 mg/L) might cause deterioration. Such a phenomenon has been reported in hyperactive children receiving low and high doses of stimulant medication.[22]

Subject recruitment is always an issue in a small medication study such as this. All such studies suffer from a volunteer effect that influences who will participate. In our study, for example,

approximately 50% of those families approached refused participation. Of those, three parents refused because they felt their children had negative reactions to theophylline; other parents refused because they saw no side effects from their child's medication and therefore no benefit to participation. This suggests that the subjects in this study are representative of a population of children whose parents had enough concern to participate but had not come to a definite conclusion concerning the side effects of theophylline. One could argue that such a sample represents the general population of children receiving intermittent theophylline treatment, since the current availability of alternative medications makes it easy to change to another medication should theophylline have obviously negative side effects for an individual child.

A further limitation of this study is that behavior and learning were only assessed over a 3½-day period. The literature cited earlier, however, suggested that side effects would be most likely to appear during the induction phase of the medication.

Another potential problem is the fact that the theophylline levels within the study group ranged from below optimal therapeutic to high therapeutic levels. Although it has been shown that most children with asthma would benefit somewhat from a theophylline level of between 7 and 10 mg/L, which is the range for most of the children in this study, it is possible that the low levels that occurred in some of the patients did not evoke the side effects of theophylline evident at higher therapeutic levels (10 to 20 mg/L). However, the lack of correlation in this study between theophylline levels and behavioral change does not support this hypothesis.

All studies, including this one, that purport to study learning do, at best, study only short-term laboratory measures of learning and not what one usually means by learning. One could not really evaluate learning change in less than a three-month period and, to our knowledge, no study of theophylline's side effects has been nearly of such duration.

Finally, the small sample size does not provide the power to detect relatively subtle effects; thus, the failure to find such effects may reflect a "type 2 error." However, almost all of the analyses fell far short of statistical significance and there was an apparently random occurrence of positive and negative medication effects. Therefore, the data from this sample provided no evidence of a clear trend toward decreased performance while taking theophylline.

In conclusion, although we originally performed this study to identify and elucidate behavioral or cognitive side effects associated with theophylline, we found essentially no decrements of behavior or learning as documented by parent or teacher questionnaires or by extensive neuropsychological tests. These findings do not agree with the reported negative effects of theophylline of several recent studies whose conclusions may have markedly changed the current treatment of childhood asthma. A large, well-controlled study of the side effects of theophylline is needed to provide an adequate guide for future treatment patterns.

This investigation was supported by a grant from The Milton Fund, Harvard University.

Theo-Dur tablets and placebo were provided by Key Pharmaceuticals, Kennilworth, NJ.

We thank Anil Kothari, MS, for preparation and randomization of the theophylline and placebo, and Nancy Scully for preparation of this manuscript.

References

1. Ellis EF: Allergic disorders, in Vaughn V, McKay R, Behrman R (eds): *Nelson's Textbook of Pediatrics.* Philadelphia, WB Saunders Co, 1979, pp 627-635.

2. Weinberger MM, Bronsky EA: Evaluation of oral bronchodilator therapy in asthmatic children. *J Pediatr* 1974;84:421-427.

3. Rall TW: Central nervous system stimulants: The xanthines, in Gilman GG, Goodman LS, Gilman A (eds): *The Pharmacologic Basis of Therapeutics,* ed 6. New York, Macmillan Publishing Co Inc, 1980, pp 592-607.

4. Rapoport JL, Berg CJ, Ismond DR, et al: Behavioral effects of caffeine in children: Relationship between dietary choice and effects of caffeine challenge. *Arch Gen Psychiatry* 1984;41:1073-1079.

5. Furukawa CT, Shapiro GG, DuHamel T, et al: Learning and behavior problems associated with theophylline therapy. *Lancet* 1984;1:621.

6. Springer C, Goldenberg B, Ben Dou I, et al: Clinical physiologic and psychologic comparison of treatment by cromolyn or theophylline in childhood asthma. *J Allergy Clin Immunol* 1985;76:64-69.

7. Rachelefsky GS, Wo J, Adelson J, et al: Behavior abnormalities and poor school performance due to oral theophylline usage. *Pediatrics* 1986;78:1133-1138.

8. Murphy MB, Dillon A, Fitzgerald MX: Theophylline and depression. *Br Med J* 1980;281:1322.

9. McLaughlin J, Nall M, Isaaca B, et al: The relationships of allergies and allergy treatment to school performance and student behavior. *Ann Allergy* 1983;51:506-510.

10. Joad JP, Ahrens MD, Lindgren SD, et al: Extrapulmonary effects of maintenance therapy with theophylline and inhaled albuterol in patients with chronic asthma. *J Allergy Clin Immunol* 1986;78:1147-1153.

11. Werry J, Sprague R, Cohen M: Connors' Teacher Rating Scale for use in drug studies in children: Empirical study. *J Abnorm Child Psychol* 1975;3:217-229.

12. Levine MD: *ANSER System.* Cambridge, Mass, Educator's Publishing Service, 1980.

13. Reynold CR, Richmond BO: What I think and feel: A revised measure of children's manifest anxiety. *J Abnorm Child Psychol* 1978;6:271-280.

14. Kimura D, McGlone J: *Neuropsychology Test Procedures.* London, Ontario, University Hospital, 1979, pp 38-39.

15. Wechsler D: *Wechsler Intelligence Scale for Children-Revised.* New York, The Psychological Corporation, 1957.

16. Kagen J, Rosman BL, Day D, et al: Information in the child: Significance of analytic and reflective attitudes. *Psychol Monogr* 1964;78:1-37.

17. *Porteus Tests Vineland Revision.* New York, The Psychological Corporation, 1978.

18. Milavetz G, Vaughn L, Weinberger MM, et al: Evaluation of a scheme for establishing and maintaining dosage of theophylline in ambulatory patients with chronic asthma. *J Pediatr* 1986;109:351-354.

19. Elkins RN, Rapoport JL, Zahn TP, et al: Acute effects of caffeine in normal prepubertal boys. *Am J Psychiatry* 1981;138:178-183.

20. Hendeles L, Weinberger MM, Bigley L: Disposition of theophylline after a single intravenous infusion of aminophylline. *Am Rev Respir Dis* 1978;118:97-103

21. Kirk RE: *Experimental Design: Procedures for the Behavioral Sciences.* Belmont, Calif, Wadsworth Publishing Co, 1968, p 246.

22. Sprague RL, Sleater EK: Methylphenidate in hyperkinectic children: Differences in dose effects on learning and social behavior. *Science* 1977;198:1274-1276.

Quotables

Self-deception: *Men, not having been able to cure death, misery, and ignorance, have imagined to make themselves happy by not thinking of these things.*

BLAISE PASCAL

Don't Forget!

Send for the latest edition of the free Consumer Information Catalog. ☐ The Catalog lists over 200 selected federal publications of consumer interest on subjects like health, nutrition, federal benefits, money management. ☐ The Catalog is free and so are many of the booklets. ☐ Just send your name and address, no strings attached. Write today:

Consumer Information Catalog

Consumer Information Center
Department DF
Pueblo, Colorado 81009

A public service of this publication and the Consumer Information Center of the U.S. General Services Administration.

Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia
Harold Levine, MPA, Galveston, Tex
Barbara Starfield, MD, Baltimore
Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of health in children.

Editorial Comment.—*Most of us prepare booklets for parents at one time or other. How useful are they? In this article, Laine et al evaluated the effectiveness of such a booklet, which they used for parents whose children received parenteral nutrition. Apparently, such efforts are not unrewarded. See what you think.*—H.D.A.

An Educational Booklet Diminishes Anxiety in Parents Whose Children Receive Total Parenteral Nutrition

Laura Laine, MEd, RD; Robert J. Shulman, MD; Kay Bartholomew, MPH;
Pat Gardner, RN; Theresa Reed, RN; Sally Cole, RN

• A major cause of anxiety in parents of hospitalized children is insufficient information about hospital procedures. In an effort to determine the extent to which parental anxiety could be diminished and knowledge and satisfaction enhanced in regard to total parenteral nutrition (TPN), we developed a booklet that describes the mechanics of TPN administration and related procedures. When informal discussions were held between parents and members of the nutritional support team during four alternating periods (every five to six months), parents of first-time recipients of TPN either did not receive the booklet (period 1, n = 20; period 3, n = 30) or received it (period 2, n = 23; period 4, n = 27). Within one week of TPN initiation, parents in both groups completed the Spielberger State-Trait anxiety scale, an attitude questionnaire, and a quiz on TPN. No differences between groups were found in ethnic background, socioeconomic status, severity of illness, age of children, or route of TPN administration. Predisposition to anxiety was also similar between the groups. In contrast, acute situational anxiety was significantly greater in the group with no booklet than in the booklet group. Parents in the no-booklet group demonstrated less comfort in the care of their children and less knowledge about TPN than did the booklet group. Written information provided to parents decreased their anxiety and increased satisfaction with patient care more successfully than did verbal communication. Such a booklet may reduce parentally induced anxiety in the child and facilitate parent-hospital staff interactions.

(*AJDC* 1989;143:374-377)

Accepted for publication Oct 20, 1988.

From the Office of Educational Resources, Texas Children's Hospital (Drs Laine and Shulman and Mss Bartholomew, Gardner, Reed, and Cole), and the US Department of Agriculture/Agriculture Research Service Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine (Dr Shulman), Houston.

Reprint requests to 6608 Fannin, Suite 601, Houston, TX 77030 (Dr Shulman).

Illness and hospitalization result in anxiety, stress, and a loss of independence.[1] Such feelings are exacerbated when intravenous feedings via total parenteral nutrition (TPN) are required, because normal feeding patterns are disrupted. The act of eating satisfies both nutritional and social needs for the child and, in addition, meets the nurturing needs of the parent. The mechanics of TPN feedings and interference with normal eating patterns, combined with illness and hospitalization, may provoke anxiety in parents as well as in the hospitalized child.

Feelings of anxiety emerge as individuals are confronted with stress from unpredictable consequences or uncertainty.[2] Anxiety may decrease the ability to perceive, think, judge, decide, and learn.[3] Parental anxiety over their child's hospitalization also may produce anxiety in the child.[4-7] Research suggests that anxiety may be reduced when parents are sufficiently informed and can predict upcoming events.[5-9] Additionally, parents who understand hospital procedures can offer more reassurance to their child.[6,10]

To reduce parental anxiety related to the hospitalization experience, particularly that associated with the use of TPN, we developed an educational booklet. The booklet explains TPN and TPN-related procedures and complications. It also describes the roles of mem-

bers of the nutritional support team (NST). We intended that the book provide a basis for questions about TPN and encourage parents to participate actively in support of their child who is receiving TPN. We anticipated that the booklet would enhance parental knowledge and awareness in regard to TPN, and thus reduce anxiety in reference to the child's care.

Previous studies have suggested that systematic preparation for hospitalization through verbal communication should reduce parental anxiety.[5,11] However, the efficacy of written educational materials has not been substantiated. Therefore, we evaluated the extent to which the TPN booklet diminished parental anxiety, enhanced knowledge, and increased satisfaction with the child's care. We compared booklet usage with the informal discussions usually held between members of the NST and parents.

MATERIALS AND METHODS

Description of the Booklet

Members of a multidisciplinary group that included physicians, dietitians, nurses, pharmacists, a psychologist, occupational and physical therapists, and health educators developed the TPN booklet. The 25-page booklet contains detailed descriptions of the mechanics of TPN administration, ie, types of catheters, catheter insertion, and the composition of the TPN solution. The roles of the various NST members are discussed, as are the various categories of physicians who work in a teaching hospital. Hospital procedures and their rationale are described, eg, chest roentgenograms, urine and blood tests, intake and output records, vital signs, dressing changes, and anthropometric measurements. The authors describe the experience of TPN and the possible effects of being connected to tubing and an infusion pump. Suggestions are made by which parents may aid in sustaining the normal feedings and behavior of their child. The importance of oral stimulation, dental care, exercise, growth, and development are reviewed, and possible TPN-related complications are addressed. The booklet also contains a glossary of items. Parents are encouraged to explain information in the booklet to their child, and to ask questions of the NST members. The booklet is written in lay language at a sixth-grade level.

Study Design

Because simultaneous randomization of parents to no-booklet and booklet groups could have resulted in dissemination of booklet information to parents in the no-booklet group, a comparative design was used. Four alternating study periods of five to six months were designated as follows: period 1, no booklet (n = 20); period 2, booklet (n = 23); period 3, no booklet (n = 30); and period 4, booklet (n = 27). To ensure that the no-booklet groups were unaware of the booklet, no parents were enrolled for one month between the booklet and no-booklet study periods. Informal discussions about TPN were held by members of the NST with all groups during formal NST rounds twice weekly. The usual care and quality of service were provided to all groups by hospital and NST personnel. Accurate information, including a brief explanation of TPN, its purpose, and the various procedures involved with its administration, was also given by all NST personnel in their daily contacts with patients. An attempt was made to reach all parents of children who received peripheral- or central-vein TPN for the first time.

Parents in both groups received the assessment packet (see the "Testing Procedure" section) within one week of the informal discussion with the NST member. The discussion took place during the first week that the child received TPN. Also during the first week, the booklet was distributed to parents in the booklet group by an NST member or by a research assistant from the Office of Educational Resources.

Background data on each patient were collected from the patient's medical record. These data included age, sex, race, payment status, diagnosis, clinical status, route of TPN administration, pre-TPN hospital stay, and number of previous hospital admissions. These variables were assessed to ensure comparability between comparison groups in regard to factors possibly related to stress and anxiety.

The protocol was approved by the Institutional Review Boards of Baylor College of Medicine and Texas Children's Hospital, Houston. Written, informed consent was obtained from the parents.

Testing Procedure

The assessment packet included the Spielberger State-Trait Anxiety Scale (STAI), an attitude questionnaire, and a quiz on TPN. The STAI measures the degree to which persons are predisposed to anxiety (stable anxiety traits), as well as acute situational anxiety levels (anxiety state).[12] Each scale contains 20 items that describe symptoms of anxiety (eg, "I feel tense") or indicate the absence of anxiety (eg, "I am relaxed").[13,14] The STAI-A-Trait Scale requires parents to report how they usually feel by indicating on a four-point Likert scale (ie, almost never, sometimes, often, almost always) the frequency with which they have experienced specific anxiety symptoms.[13,14] The STAI-A-State Scale requires parents to indicate the intensity of their feelings of anxiety at a particular moment by rating themselves on a four-point Likert scale (ie, not at all, somewhat, moderately so, very much so).

The attitude questionnaire assessed the parents' comfort with the child's care in regard to TPN and assessed their satisfaction with their own knowledge of TPN and its related procedures and complications. The questionnaire consisted of nine questions that required responses on a three-point Likert scale (ie, very well, fairly well, not well). The questionnaire was found to be reliable by item analysis.[15] Cronbach's α reliability coefficients for the questions regarding "comfort with care" (0.82) and "satisfaction with own knowledge of TPN" (0.84) indicated internal consistency within these sets of questions (ie, reliability in measurement of the one concept intended for each question set).

The TPN quiz comprised 30 multiple-choice questions that addressed topics discussed in the TPN booklet. The quiz was composed by selected members of the multidisciplinary group. Quiz content validity was further evaluated and modified by the entire group who collaborated on the development of the TPN booklet. Cronbach's α reliability coefficient for the total quiz was 0.85. There was good correlation between individual items and the total quiz.

Statistics

Differences between groups were compared by analysis of covariance using the treatment group (ie, no booklet vs booklet), period of study (ie, 1, 2, 3, or 4), and possible interactions related to study period as covariates. Differences in proportions between groups were determined using χ^2 analysis.

RESULTS

No significant differences were detected between groups in regard to age, sex, race, payment status, children with previous hospital admissions, pre-TPN hospital stay, type of illness, clinical status, or route of TPN administration (central vs peripheral vein) (Table 1).

Trait anxiety scores were similar between the no-booklet and booklet groups (Table 2). In contrast, state anxiety scores were significantly higher in the no-booklet group than in the booklet group (Table 2).

The scores for the satisfaction-with-care portion of the attitude question-

Table 1.—Demographic Profile of Patients Receiving Total Parenteral Nutrition (TPN)

	Group	
	No Booklet (n=50)	Booklet (n=50)
Mean ± SD age, y (median)	4.5 ± 5.4 (1.7)	5.0 ± 6.3 (0.8)
Sex, No. M	26	25
Race, No. of patients		
White	35	41
Black	10	5
Hispanic	5	4
Payment status, No. of patients		
Private	41	44
Medicaid	3	3
Charity	6	3
Previous admissions*	31	29
Mean ± SD pre-TPN hospital stay, d (median)	5.0 ± 4.7 (4)	6.6 ± 9.3 (4)
No. of patients with chronic illness	31	28
Clinical status, No. of patients		
Good	20	18
Fair	19	22
Poor	11	10
TPN given in central vein, No. of patients	39	40

*Number of patients with a previous hospitalization.

Table 2.—Test Scores

	Mean ± SD Score		
Test	No-Booklet Group (n=50)	Booklet Group (n=50)	P
Anxiety Trait	52.1 ± 9.1	52.0 ± 12.3	Not significant
Anxiety State	59.5 ± 9.9	53.6 ± 12.0	.005
Comfort with care	6.5 ± 1.7	7.9 ± 1.3	.001
Satisfaction with knowledge	13.0 ± 2.9	15.1 ± 2.4	.001
Total parenteral nutrition quiz*	25.6 ± 16.0	6.6 ± 7.7	.0001

*Percent of questions answered incorrectly.

naire and scores for satisfaction with knowledge of TPN were significantly lower for parents in the no-booklet group than for parents in the booklet group (Table 2). Sixteen percent of parents in the no-booklet group read some material on TPN. In contrast, 78% of parents in the booklet group read the booklet. Seventy-seven percent of parents in the no-booklet group spoke with their children (>2 years old, n=25) about TPN, whereas all parents in the booklet group discussed TPN with their children (>2 years old, n=24; $P<.05$). In the written comment section of the test, parents in the no-booklet group requested information on TPN and related procedures and complications, growth expectations, and coping skills for themselves and their children. The booklet group reported that they were well informed, but would have liked the information before central venous catheter placement or TPN initiation. They also requested information on other topics, such as cystic fibrosis, prematurity, surgery, various cancers, and necrotizing enterocolitis.

Scores on the TPN quiz were significantly lower for parents in the no-booklet group than for those in the booklet group (Table 2). No questions were answered consistently incorrectly by either group.

COMMENT

Our booklet was developed to encourage an understanding of the need for nutritional support, TPN, and the rationale for TPN-related procedures. Results of an earlier study support the hypothesis that parents and children who receive systematic preparation and supportive care, in contrast to those who do not, will be less anxious and more cooperative in the hospital.[11] As a consequence, we anticipated that parent-staff or parent-physician interactions would be enhanced.

Our study demonstrated a significant decrease in acute situational anxiety among parents of a hospitalized child who received a booklet that described TPN. Our data, therefore, support the concept that systematic preparation can diminish anxiety.[5,11] The communication of accurate information may diminish anxiety because it enables parents to anticipate events and allows for accurate expectations.[5-9] Results of a study by Skipper et al[5] support the hypothesis that a mother's level of anxiety can be decreased through the provision of information and emotional support. In contrast with our study, however, experimental manipulations in the study by Skipper and colleagues[5] involved only verbal communication of information. The control group in our study received verbal information only. The provision of both verbal and written information diminished acute situational anxiety more effectively than verbal information alone (Table 2).

Our study indicated that parents in the booklet group were more satisfied with the information they received and more comfortable with their knowledge of nutritional support than parents in the no-booklet group (Table 2). Skipper et al[5] and Wolfer and Visintainer[11] reported satisfaction among parents who were systematically prepared for the hospitalization of their children, but these investigators used verbal communication only. In interviews of 25 mothers regarding the hospital experience of their children, mothers stressed repeatedly that the reason for their anxiety

was the lack of information regarding diagnosis, procedures, and treatments.[10] In our study, parents in the booklet group indicated that they were well informed, but that they would have preferred to have received the information earlier. Gofman et al[16] reported in 1957 that parents had indicated that they would appreciate written information for reference at home, in addition to oral explanations from the physician. Parents in the booklet group of our study requested written materials in areas of care other than nutritional support, further emphasizing their need for information, particularly written material. Parents in the no-booklet group, however, requested comprehensive information on TPN.

Parents in the booklet group scored significantly higher on the TPN quiz than those in the no-booklet group (Table 2), which suggests that the written materials were more effective in enhancing parents' knowledge of nutritional support. Gofman et al[16] referred to statements by parents that suggested that they were nervous, forgot to ask questions, and were too upset to listen. A well-constructed educational booklet provides parents with information to read at their leisure.

Educational materials supplied to the parents, eg, the TPN booklet, may reduce parentally induced anxiety in the child. Indeed, all parents in our study who reviewed the booklet stated that they had discussed the information with their children. Researchers agree generally that a major source of anxiety in the child arises from their parents' fears.[7,17] The "contagion theory," often referred to in the literature, suggests that anxiety is transferable, especially in the parent-child relationship.[5,7,17,18] When parental anxiety is diminished, parental coping skills improve; thus parents can aid their child in containing his or her own fears. Parents can then describe the hospital setting and the procedures in accurate, understandable terms to their child, diminishing the threatening nature of the hospital experience, and ultimately lessening the child's anxiety.[5,11,16,19]

In conclusion, our study supports previous findings that suggest that information provided to parents will decrease their anxiety. Importantly, our results extend these observations by demonstrating that written materials (ie, the TPN booklet) were more successful than verbal communication alone, not only in decreasing parental anxiety, but also in improving satisfaction with their child's care.

This work is a publication of the US Department of Agriculture/Agriculture Research Service Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston. This project has been funded in part with federal funds from the US Department of Agriculture/Agricultural Research Service under cooperative agreement 58-7MNI-6-100.

The contents of this publication do not necessarily reflect the views or policies of the US Department of Agriculture, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

We thank the members of the Multidisciplinary TPN Education Group; J. Kenneth Fraley, MPH, and E. O'Brian Smith, PhD, for help in the statistical analyses; Robert E. Reichlin, PhD, for review of the manuscript; Danita Czyzewski, PhD, for review of the manuscript and interpretation of the anxiety scale; E. Roseland Klein for editorial review; and Donna M. Reid for manuscript preparation.

References

1. Bayer LM: Psychosocial responses of adult patients to nutritional support. *Nutr Support Serv* 1984;4:40-43.
2. May R: *The Meaning of Anxiety*, ed 2. New York, WW Norton & Co Inc, 1977.
3. Travelbee J: *Interpersonal Aspects of Nursing*. Philadelphia, FA Davis Co, 1973.
4. Neylan M: Anxiety. *Am J Nurs* 1962;62: 110-111.
5. Skipper JK, Leonard RC, Rhymes J: Child hospitalization and social interaction. *Med Care* 1968;6:496-506.
6. Smitherman CH: Parents of hospitalized children have needs, too. *Am J Nurs* 1979;79:1423-1424.
7. Bright F: The pediatric nurse and parental anxiety. *Nurs Forum* 1965;4:31-47.
8. Mason E: The hospitalized child: His emotional needs. *N Engl J Med* 1965;272:406-414.
9. Condon SR: Daytime hospital for children. *Am J Nurs* 1972;72:1431-1433.
10. Frieburg KH: How parents react when their child is hospitalized. *Am J Nurs* 1972;72:1270-1272.
11. Wolfer JA, Visintainer MA: Pediatric surgical patients' and parents' stress responses and adjustment as a function of psychologic preparation and stress-point nursing care. *Nurs Res* 1975; 24:244-255.
12. Kendall PC: Anxiety: States, traits-situations? *J Consult Clin Psychol* 1978;46:280-287.
13. Spielberger CD, Barker LR, Donham GW, et al: The factor structure of the state-trait anxiety inventory, in Sarason IG, Spielberger CD (eds): *Stress and Anxiety*. Washington, DC, Hemisphere Publishing Co, 1980, pp 95-109.
14. Spielberger CD: *Manual for the State Trait Anxiety Inventory*. Palo Alto, Calif, Consulting Psychologists Press, 1983.
15. *SPSS Users Guide*, ed 2. New York, McGraw-Hill International Book Co, 1986.
16. Gofman H, Buckman W, Schade GH: Parents' emotional response to child's hospitalization. *AJDC* 1957;93:629-636.
17. Korsch BM: Psychologic principles in pediatric practice: The pediatrician and the sick child, in Levine SZ (ed): *Advances in Pediatrics*. Chicago, Year Book Medical Publishers Inc, 1958, pp 11-25.
18. Blom GE: The reactions of hospitalized children to illness. *Pediatrics* 1958;22:590-600.
19. Goshman B, Yunck M: Dealing with the threats of hospitalization. *Pediatr Nurs*, September, 1979, pp 32-35.

In Other AMA Journals

JAMA

Reducing the Illegal Sale of Cigarettes to Minors

D. G. Altman; V. Foster; L. Rasenick-Douss; J. B. Tye (*JAMA*. 1989;261:80)

Trust is more than a matter of taste.

Trust is knowing that your recommendation stands for efficacy. Dimetapp Elixir has a heritage of efficacy that's unsurpassed for colds and allergy relief. Every spoonful provides effective relief of the runny nose, sniffling and nasal congestion of a cold or flu. Dimetapp Elixir also relieves the itchy, watery eyes and sneezing of little allergy sufferers.

And, Dimetapp is a name that has always stood for great grape taste. So, compliance is never an issue. Trust Dimetapp Elixir. A heritage of efficacy in every good-tasting spoonful.

Dimetapp® Elixir

Nasal Decongestant/Antihistamine

A heritage of efficacy in every spoonful.

© 1989 A.H.Robins Company

Radiological Case of the Month

Andrew L. Weisberg, MD; Jack O. Haller, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A previously asymptomatic 10-year-old girl presented to Kings County Hospital, Brooklyn, NY, with a history of a left-thigh mass. There was no history of trauma. On physical examination a tender, solid, soft-tissue mass (2.5×4.5 cm) was noted in the anterior compartment of the left thigh, 10 cm proximal to the knee. The skin over the mass was normal. The mass was immovable, and it was not clinically possible to determine its relationship to the muscle. The child had no rash, fever, or systemic complaints, and results of all routine laboratory studies were normal. T_1-weighted (Fig 1) and T_2-weighted (Fig 2) magnetic resonance images (MRIs) of the thighs were obtained.

Accepted for publication March 11, 1988.
Contributed from the Department of Radiology, Downstate Medical Center, Brooklyn, State University of New York.
Reprint requests to the Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Figure 1.

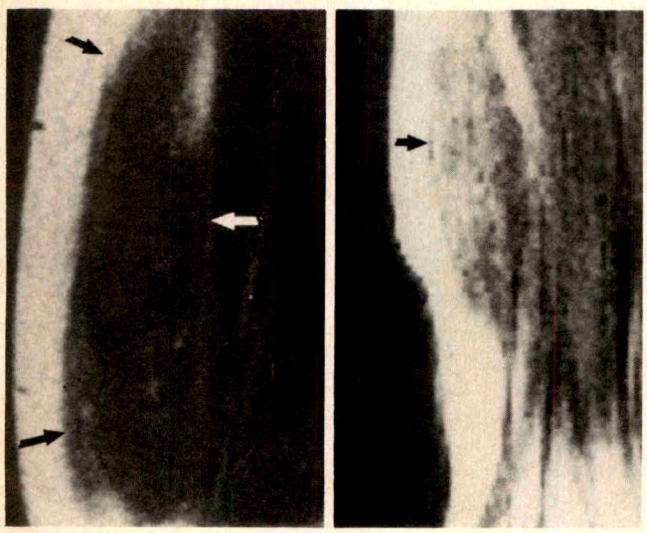
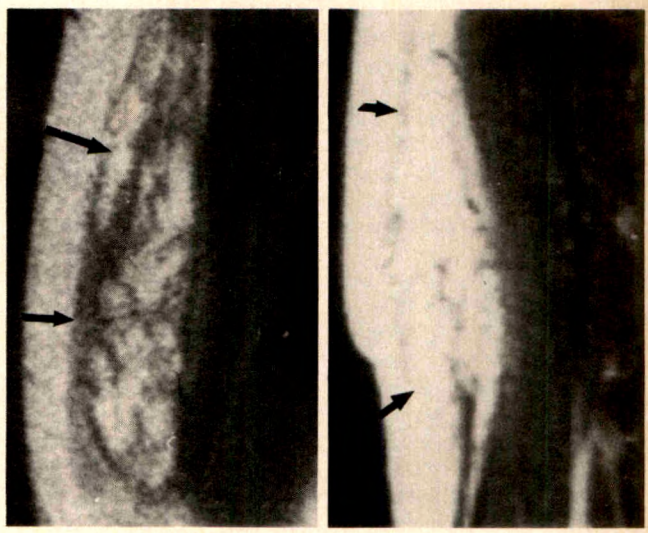


Figure 2.



The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Denouement and Discussion

Hemangioma of the Thigh

Fig 1.—T_1-weighted frontal (left) and lateral (right) views of left thigh (arrows) show inhomogeneous signal, which is different from normal muscles.

Fig 2.—T_2-weighted frontal (left) and lateral (right) views of left thigh show intense signal from the anteromedially located mass (arrows). Mass is well delineated and has serpiginous appearance.

The hemangioma is one of the most common vascular tumors. The majority are cutaneous and are discovered at birth or during early infancy. Cutaneous hemangiomas are often asymptomatic and regress spontaneously before age 7 years.[1] Their obvious clinical manifestations require no imaging workup.

Skeletal muscle hemangiomas are uncommon tumors that are detected later in childhood or in early adult life. They usually present as deep soft-tissue masses and have a predilection for the lower limbs. They are readily diagnosable if associated with overlying cutaneous purpuric discoloration, a pulsatile mass with a bruit, or dilated veins.[2] Unfortunately, most skeletal muscle hemangiomas do not have these features, and over 90% are misdiagnosed preoperatively.[3]

Although hemangiomas are benign lesions, they can have deleterious consequences through mass effect (ie, if located in the central nervous system, adjacent to the airway, or through erosion of bone). Reports of life-threatening sequelae, including cardiac failure secondary to arteriovenous shunting, consumptive coagulopathy (Kasabach-Merritt syndrome), or gangrene, are uncommon. Cosmetic deformity from growth discrepancy, osteolysis, or Klippel-Trenaunay-Weber syndrome have major psychosocial impact.[4]

The literature concerning these vasoformative lesions is filled with confusing nomenclature. The largest group are capillary hemangiomas. Microscopically, they appear as a disorganized array of capillaries with occasional mitotic cells interlaced with fibrous stroma. An early proliferative phase is characterized by dilation of the vascular channels and flattening of the endothelium. They involute as fibroblastic activity and thrombus formation occur.[5]

The cavernous variety is larger and found in deeper locations. Histologically, they are dilated blood cavities with a compressed endothelial lining. They, too, may thrombose and undergo dystrophic calcification but are less likely to involute.[6]

In recent years, computed tomography (CT), nuclear scanning, and angiography have been complementary modalities for the workup of these deep-seated soft-tissue masses. Magnetic resonance imaging has now supplanted them as the imaging modality of choice.

Whereas CT can depict the size of the hemangioma and its margins, its tendency to underestimate tumor extent and the requirement for intravenous contrast to visualize the deep vascular bundles are drawbacks.[7]

The CT scan results are often nonspecific. Hemangiomas may exhibit marked enhancement. This enhancement may be either heterogeneous or homogeneous.[8] There is argument as to whether homogeneous enhancement correlates with the growth phase and mixed attenuation with a degenerative phase (replacement of muscle tissue with fibrofatty matrix).[9] The calcification pattern on a CT scan is specific only if a rounded laminated structure called a phlebolith is demonstrated. However, less specific amorphous and curvilinear calcification also occurs. Furthermore, hemangiomas appear as ill-defined soft-tissue masses belying their benign nature.

Angiography is more specific and can differentiate hemangiomas, arteriovenous malformations, and venous malformations. Angiography is considered invasive, and if the "classic" fine-caliber homogeneously opacified vessels are not seen, the benignity of tissue masses cannot be confirmed, and the patient must then undergo a tissue aspiration to establish the diagnosis.[3,9]

Magnetic resonance imaging appears to have the highest sensitivity and specificity; MRI has superior tissue resolution, allowing for differentiation of the thin, delicate intramuscular fat plans between the large muscle groups. The patient is spared ionizing radiation and intravenous contrast. On both T_1- and T_2-weighted images, one is able to differentiate a higher signal intensity and "serpiginous pattern mass" considered pathognomonic of hemangiomas. (Normal muscle has lower signal intensity.) The multiplanar capability affords greater delineation of tumor extent, thereby facilitating operative planning. The sharp, crisp margins of hemangiomas on MRI enable us to confidently differentiate them from malignant processes that tend to infiltrate surrounding fat, transgress several muscle compartments, and invade bone.[10,11] The findings of (1) a sharply marginated serpiginous soft-tissue mass, (2) associated atrophy of surrounding muscles, and (3) signal intensity lower than subcutaneous fat on T_2-weighted images are sufficient to forego tissue biopsy for diagnosis.

A high index of suspicion for hemangiomas must be maintained whenever a soft-tissue mass is noted in the muscles of the appendicular skeleton. Magnetic resonance imaging can differentiate hemangiomas from lipomas, hernias, hematomas, soft-tissue sarcomas, and lymphomas.

References

1. Behrman RE, Vaughan VC (eds): *Nelson Textbook of Pediatrics*, ed 13. Philadelphia, WB Saunders Co, 1987, pp 1108, 1370-1371.
2. Silverman FN (ed): *Caffey's Pediatric X-ray Diagnosis*, ed 8. Chicago, Year Book Medical Publishers Inc, 1984, vol 1, pp 876-877.
3. Richardson ML, Kilcoyne RF, Gillespy T, et al: Magnetic resonance imaging of musculoskeletal neoplasms. *Radiol Clin North Am* 1986;24:259-267.
4. Allen PW, Enzinger FM: Hemangioma of skeletal muscle: An analysis of 89 cases. *Cancer* 1972;29:8-22.
5. Allen PW: The fibromatoses: A clinicopathological classification based on 140 cases. *Am J Surg Pathol* 1977;1:255-270.
6. Rich PJ, King W: Benign cortical hyperostosis underlying soft-tissue tumors of the thigh. *AJR* 1982;138:419-422.
7. Daneman A: *Pediatric-Body CT.* New York, Springer-Verlag NY Inc, 1987, pp 316-319.
8. Takayasu K, Moriyama N, Shima Y, et al: Atypical radiographic findings in hepatic cavernous hemangiomas: Correlation with histologic features. *AJR* 1986;146:1149-1153.
9. Petasnick JP, Turner DA, Charters JR, et al: Soft tissue masses of the locomotor system: Comparison of MR imaging with CT. *Radiology* 1986;160:125-133.
10. Enzinger FM, Weiss SW: *Soft Tissue Tumors.* St Louis, CV Mosby Co, 1983, pp 379-421.
11. Totty WG, Murphy WA, Lee JKT: Soft tissue tumors: MR imaging. *Radiology* 1986;160:135-141.

Picture of the Month

Mary E. Rimsza, MD, (*Contributor*); Murray Feingold, MD (*Section Editor*)

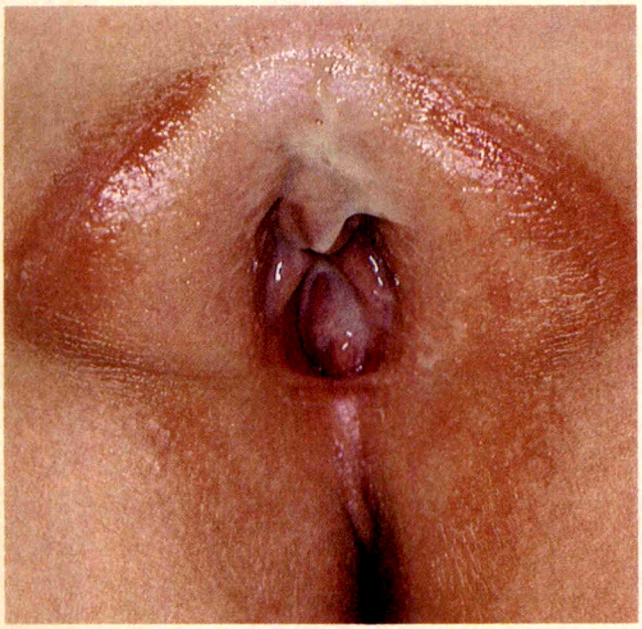


Figure 1.

Figure 2.

The statements listed below are best associated with which of the above figures:

(*a*) This disorder may be successfully treated with estrogen cream.

(*b*) Primary amenorrhea in adolescence is a presenting symptom.

(*c*) Patients with this condition should be reported to the public health department and a child protective agency.

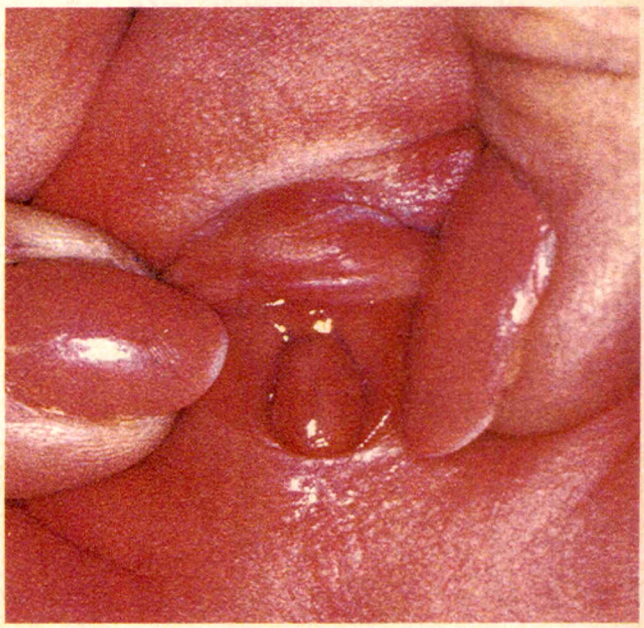


Figure 3.

Accepted for publication July 12, 1988.

Contributed from the Department of Pediatrics, Maricopa Medical Center, Phoenix.

Reprint requests to National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—Gonorrheal vulvovaginitis.

Fig 2.—Labial fusion (adhesion of labia minora).

Fig 3.—Imperforate hymen.

(*a*) Labial fusion is the partial or complete adherence of the labia minora (Fig 2). It most likely develops secondary to denudation of the upper squamous epithelial layer of the labial mucosa with formation of a thin connective-tissue bridge. Adhesion of the labia minora occurs in women with low estrogen levels, prepubescent girls, and postmenopausal women. Inflammatory conditions such as vulvitis, diaper dermatitis, and trauma may be important predisposing factors. Labial adhesions can be separated manually or with the use of an estrogen cream.

(*b*) Normally the hymen is a membranous diaphragm with a central orifice, but occasionally the hymenal membrane is imperforate (Fig 3). If an imperforate hymen is not detected in the newborn period, the patient will present at puberty with primary amenorrhea and hematocolpos. Occasionally a newborn with an imperforate hymenal membrane develops hydrocolpos because of retained vaginal and cervical secretions that are the result of passive maternal hormonal stimulation. In most cases, however, the newborn with an imperforate hymen is asymptomatic.

(*c*) Gonorrheal vulvovaginitis in prepubertal girls is usually characterized by vulvovaginal erythema and a thick, yellowish, purulent discharge (Fig 1). The neutral to alkaline pH and thin, atrophic, noncornified epithelium of the immature vagina encourage a diffuse vaginitis and dysuria. Although salpingitis, perihepatitis, and peritonitis have been reported in children, these complications are rare. Since most children under 10 years of age will have been infected via involuntary sexual contact, a complete medical and social evaluation is indicated. Because the source of the infection is often a family member, all family members should be cultured for gonorrhea. The committee on Early Childhood, Adoption, and Dependent Care of the American Academy of Pediatrics recommends that prepubertal gonorreal infections be reported to protective agencies and the public health department.

References

1. American Academy of Pediatrics: Committee on Early Childhood, Adoption, and Dependent Care: Gonorrhea in prepubertal children. *Pediatrics* 1983;71:553.
2. Neinstien LS, Goldenring J, Carpenter S: Nonsexual transmission of sexually transmitted diseases: An infrequent occurrence. *Pediatrics* 1984;74:67.
3. Capraro VJ, Greenberg H: Adhesions of the labia minora. *Obstet Gynecol* 1972;39:65.
4. Berkowitz CD, Elvik SL, Logan MK: Labial fusion in prepubescent girls: A marker for sexual abuse? *Am J Obstet Gynecol* 1987;156:16.
5. Dickson CA, Saad S, Tesar JD: Imperforate hymen with hematocolpos. *Ann Emerg Med* 1985;14:467-469.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

SOME ALLERGY PATIENTS THINK IT'S "SAFE" TO GO INDOORS...

But it isn't. For the majority of allergy patients there is no "end" to the allergy season. The menacing house dust mite (or alternaria or cat dander) causes as much nasal discomfort as the seasonal flareups brought on by tree, grass, and weed pollens.

In fact, recent studies report that most allergic rhinitis patients suffer substantial nasal symptoms more than 40 weeks each year.[1,2]

Yet there is a way to safely and effectively offer these patients relief, year round. Proven, non-sedating, site-specific NASALCROM® Nasal Solution. It delivers rapid, symptomatic relief of nasal congestion, rhinorrhea, nose blowing, and sneezing...all with virtually no serious or complicating side effects.

NASAL SOLUTION

NASALCROM®

(cromolyn sodium/FISONS)

For allergic rhinitis...year round.

Scanning Electron Micrograph of the House Dust Mite (x300)

© Fisons Corporation 1986

DESCRIPTION: Each milliliter of NASALCROM® (cromolyn sodium nasal solution, USP) contains 40 mg cromolyn sodium in purified water with benzalkonium chloride 0.01% and EDTA (edetate disodium) 0.01%.
INDICATIONS: NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.
CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.
PRECAUTIONS: General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy.
In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.
Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.
No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.
No evidence of impaired fertility was shown in laboratory animal reproduction studies.
Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.
Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.
ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphylaxis.
Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.
CAUTION: Federal law prohibits dispensing without prescription.
References: 1. Survey results of 3,800 households containing 10,300 people, conducted by ORC (Opinion Research Corporation), March 1985. 2. Data on file, Fisons Corporation. Independent Study by DTW Market Research Group: July 1985.
NASALCROM® is a registered trademark of Fisons plc. FIS-044

FISONS

The Pediatrics Board Review Course

April 6-12, 1989 — Nashville
May 26-31, 1989 — Louisville
September 26-October 1, 1989 — Chicago
Now, your only BOARD REVIEW just before Written and Oral Exams

OBJECTIVES:
- Improve basic and clinical knowledge in pediatrics
- Assist residents and fellows in organizing study
- Prepare candidates to take examinations
- Provide practicing pediatricians with a review and update

METHODS:
- HOME STUDY MATERIALS with a syllabus of questions and answers — and assignments
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

NEONATOLOGY
Growth and Development
Nutrition
Newborn Diseases
Fluids and Electrolytes
Critical Care

IMMUNOLOGY
Immune Physiology
Immunodeficiency
Allergy
Rheumatology

INFECTIOUS DISEASES
Bacterial Infections
Viral Infections
Spirchetes and Richettsia
Mychotic Infections
Parasitic Infections

CARDIOLOGY
Cardiac Evaluation
Cyanotic Diseases
Acyanotic Diseases
Acquired Diseases

GASTROENTEROLOGY
Oral Cavity/Esophagus
Anomalies and Diseases
Malabsorption
Liver and Gall Bladder
Pancreas

NEPHROLOGY
Renal Physiology
Glomerular Diseases
Congenital Uropathies
Urology

ENDOCRINOLOGY
Hypothalamus/Pituitary
Thyroid and Parathyroid
Adrenal Disorders
Gonadal Disorders
Diabetes/Hypoglycemia

HEMATOLOGY-ONC.
Red Cell Disorders
White Cell Disorders
Platelets and Coagulation
Solid Tumors

NEUROLOGY
Convulsive Disorders
Congenital Diseases
Acquired Diseases
Neuromuscular Diseases

PSYCHOLOGY
Psychological Development
Psychiatric Disorders
Child and Drug Abuse
Mental Retardation

GENETICS AND OTHER
Chromosomal Anomalies
Errors of Metabolism
Morphologic Syndromes
Preventive Medicine
Poisoning

OTHER SPECIALITIES
Orthopedics
Dermatology
Opthalmology
Otolaryngology
Pulmonology

Limited Enrollment: PEDIATRICS BOARD REVIEW REGISTRATION

Name _____

Address _____

City/State/Zip _____

Phone _____

For: ☐ April 6-12, 1989 — Nashville
☐ May 26-31, 1989 — Louisville
☐ Sept. 26-Oct 1,'89 — Chicago

Mail today to:
1094 Dawn Lane, Dept A3
P.O. Box 2218
Terre Haute, IN 47802

☐ Check is enclosed for $ _____

☐ Please send more information.

*"Accommodations were comfortable..."**

GOALS AND LOCATION: The course is held the week before oral and written board exams. Sites are chosen for excellent study and minimal cost of hotel and travel for board candidates. Home study questions will be sent before the course. Your best value is to repeat the seminar for half price the week before both written and oral exams. Topics and faculty are upgraded for each program. Our hotel rates are typically $66 to $80 single and $80 to $98 double. Please wait for instructions before buying travel tickets.

*"...and those little extras...."**

LOWEST AIR FARES: Reliable Travel offers you the lowest air fare — often below super-saver rates. Please call toll-free 1-800-645-6504 ext. 10 and identify yourself with this Osler course for special group fares.

*"...remarkably complete and pleasant."**

PLACEMENT SERVICE: For a practice opportunity write or call (800) 356-7537.

*"...the most education for the money."**

FEES AND C.M.E. CREDITS:
- **C.M.E. Credit: 60 hrs.**
- Practicing Pediatrician: $660
- Residents and Fellows: one third off
- Repeating course within 3 years: half price
- **Add 10% within 10 days of course.**
- Attendees not in course hotel add $8/day.
- $50.00 will reserve your position.

*"...home study material was extremely helpful."**

CANCELLATIONS: Refunds subject to $50 fee, will be made until the seminar begins.
- Cancellation after mailing home study material requires retention of half of the fee.

*"I feel [the course] helped me pass the boards."**

INFORMATION:
Joseph H. Selliken Jr., M.D.
THE OSLER INSTITUTE
1094 Dawn Lane, Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

**Comments by participants of our courses*

Published by the American Medical Association

April 1989
Volume 143, Number 4

AJDC

AMERICAN JOURNAL OF DISEASES OF CHILDREN

Ambulatory Pediatric Association

29th Annual Meeting
May 1-5, 1989

Program and Abstracts

Complete Contents, p 385

Trust is more than a matter of taste.

Trust is knowing that your recommendation stands for efficacy. Dimetapp Elixir has a heritage of efficacy that's unsurpassed for colds and allergy relief. Every spoonful provides effective relief of the runny nose, sniffling and nasal congestion of a cold or flu. Dimetapp Elixir also relieves the itchy, watery eyes and sneezing of little allergy sufferers.

And, Dimetapp is a name that has always stood for great grape taste. So, compliance is never an issue. Trust Dimetapp Elixir. A heritage of efficacy in every good-tasting spoonful.

Dimetapp® Elixir

Nasal Decongestant/Antihistamine

A heritage of efficacy in every spoonful.

© 1989 A.H.Robins Company

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOL 143 NO. 4 April 1989

Copyright © 1989 by the American Medical Association

Monthly Circulation >44 500
Also published in French

ABSTRACTS

395 **Ambulatory Pediatric Association: Program and Abstracts**

412 **Annual Meeting of the Ambulatory Pediatric Association**

THE PEDIATRIC FORUM

441 **Advances in Neonatal Care**
Joel Frader, MD, Pittsburgh, Pa, Boyd W. Goetzman, MD, PhD, Davis, Calif

Incomplete Immunizations and the Computer
Vincenzo Curro, MD, Rome, Italy

Does Methylprednisolone Pulse Therapy Deteriorate the Course of Rapidly Progressive IgA Nephropathy?
Noritomo Itami, MD; Yasushi Akutsu, MD; Yukihiro Kusunoki, MD; Hiroyuki Tochimaru, MD; Yasuo Takekoshi, MD, Sapporo, Japan; Thomas R. Welch, MD; A. James McAdams, MD; Annette Berry, Cincinnati, Ohio

Parent-Child Minimal Change Nephrotic Syndrome
Alexander K. C. Leung, MBBS, FRCPC, William Lane M. Robson, MD, FRCPC, Calgary, Canada

Gonococcal Conjunctivitis Mimicking Orbital Cellulitis in a Young Adolescent
Agustin Legido, MD, Mark Joffe, MD, Philadelphia, Pa

Polymicrobial Bacteremia and Child Abuse
Jacob Amir, MD, St Louis, Mo

Risks of Placing One-Way Valves in Ventilator Circuits
Bob Demers, RRT, Stanford, Calif, Ronald W. Mike, RRT, Worcester, Mass

447 **LEADS FROM THE MMWR**

EDITORIAL

451 **Neonatal Intensive Care**
Alan D. Bedrick, MD, Tucson, Ariz

THE EDITORIAL BOARD SPEAKS...

453 **Connectedness**
Elizabeth R. McAnarney, MD, Rochester, NY

Continued on p 387.

EDITORIAL BOARD

Editor
Vincent A. Fulginiti, MD
American Journal of Diseases of Children
Dean's Office
Room 1529
Tulane University
School of Medicine
1430 Tulane Avenue
New Orleans, LA 70112
(504) 584-1989

Associate Editors
James J. Corrigan, Jr, MD
Tucson, Ariz
Alan D. Bedrick, MD
Tucson, Ariz

Book Review Editor
Peggy C. Ferry, MD
Tucson, Ariz

Administrative Assistant
Joann M. Quane
New Orleans, La

Secretary
Laura Martin
Tucson, Ariz

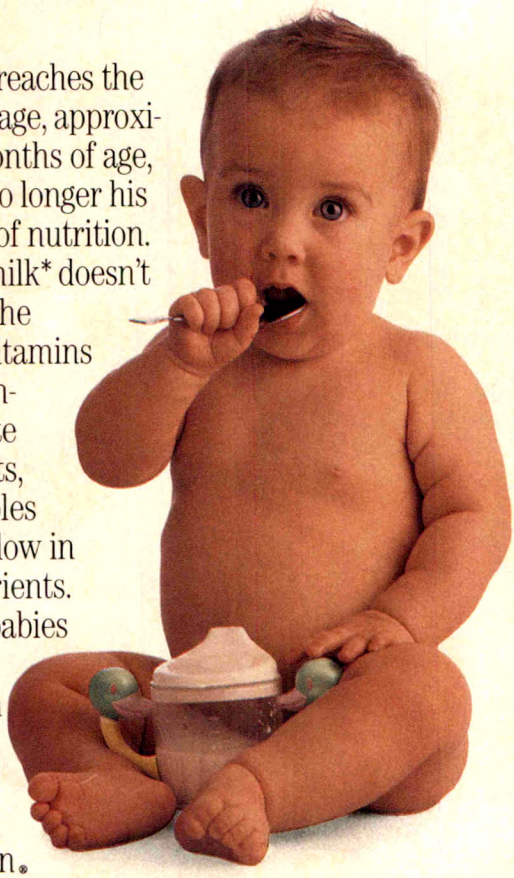
Hugh D. Allen, MD, Columbus, Ohio
Milton I. Arnold, MD, Los Angeles, Calif
Richard W. Blumberg, MD, Atlanta, Ga
Ben H. Brouhard, MD, Cleveland, Ohio
George W. Brown, MD, Los Lunas, NM
Beverly B. Dahms, MD, Cleveland, Ohio
Murray Feingold, MD, Boston, Mass
Patricia Ferrieri, MD, Minneapolis, Minn
Laurence Finberg, MD, Brooklyn, NY
Boyd W. Goetzman, MD, PhD, Davis, Calif
John D. Johnson, MD, Albuquerque, NM
James P. Keating, MD, St Louis, Mo
Elizabeth R. McAnarney, MD, Rochester, NY
Dan G. McNamara, MD, Houston, Tex
Beverly C. Morgan, MD, Orange, Calif
Henry L. Nadler, MD, Chicago, Ill
Robert Penny, MD, Los Angeles, Calif
Albert W. Pruitt, MD, Augusta, Ga
Kenneth B. Roberts, MD, Worcester, Mass
Barton D. Schmitt, MD, Denver, Colo
E. Richard Stiehm, MD, Los Angeles, Calif
William B. Strong, MD, Augusta, Ga
Beverly P. Wood, MD, Rochester, NY

CARNATION®

GOOD NATURE™

Iron Fortified Follow-Up Formula

For babies over six months of age eating solid foods



When baby reaches the solid food stage, approximately 6 months of age, formula is no longer his sole source of nutrition. Yet, whole milk* doesn't contain all the necessary vitamins and the high-carbohydrate cereals, fruits, and vegetables he eats are low in certain nutrients. And, older babies require less energy from fat[1] and more from protein.[2]

Carnation® GOOD NATURE™ Follow-Up Formula provides the added nutrients for the older baby's optimal growth and development. And it contains more protein and calcium than starter formula to support the increased metabolic demands of bone mineralization and muscle mass growth.

The ratio of unsaturated to saturated fatty acids in GOOD NATURE is 2:1. GOOD NATURE is higher in monounsaturated fatty acids yet contains 28% less fat than starter formula to satisfy the changing needs of the older baby.

GOOD NATURE also has a carbohydrate blend of 63% corn syrup solids and 37% lactose to help assure tolerance. It contains 12 mg iron per quart to help ensure a sufficient supply at an age when inborn stores are depleted. GOOD NATURE costs less than starter formula and also tastes, smells, and looks like the real food baby is learning to enjoy.

When baby is ready for solid food, Mom may ask you about GOOD NATURE Follow-Up Formula. You can reassure her that GOOD NATURE is nutritionally sound and makes good sense for her baby.

For more information about GOOD NATURE Follow-Up Formula, please write to: Carnation Nutritional Products, 5045 Wilshire Blvd., Los Angeles, CA 90036.

Carnation®
Setting the stage for better development™

GOOD NATURE Follow-Up Formula... now available to consumers in 32-fl-oz ready-to-feed fresh packs and 12-oz easy-to-mix powder canisters.

REFERENCES: 1. Kwiterovich PO Jr, Salz KM: Pediatric aspects of the diet-heart hypothesis, in Bond JT, Filer LJ, Leveile GA, et al (eds): *Infant and Child Feeding.* Academic Press, 1981, pp 283-315.
2. Food and Nutrition Board, NAS/MRC. *Recommended Dietary Allowances,* ed 9, 1980. *Pasteurized cow's milk that isn't fortified.

NP-026 3/89

Continued from p 385.

ARTICLES

454 The Effect of Weight Control on Lipid Changes in Obese Children
Leonard H. Epstein, PhD; Lewis H. Kuller, MD; Rena R. Wing, PhD; Alice Valoski, MS; James McCurley, MA, Pittsburgh, Pa

458 Efficacy of a Nonrestricted Fat Diet in Patients With Cystic Fibrosis
Elisabeth Luder, PhD; Meyer Kattan, MD; John C. Thornton, PhD, New York, NY; Kathleen M. Koehler, PhD, Albuquerque, NM; Richard J. Bonforte, MD, New York, NY

SPECIAL CONTRIBUTION

466 Adolescent Health
Elizabeth Brown, MD, William R. Hendee, PhD (*Editors*), Chicago, Ill

ARTICLES

471 Determinants of School Performance in Children With Chronic Asthma
Linda B. Gutstadt, MEd; Jerry W. Gillette, MEd; David A. Mrazek, MD; Joleen T. Fukuhara; John F. LaBrecque, PhD; Robert C. Strunk, MD, Denver, Colo

476 Cardiorespiratory Patterns During Alarms in Infants Using Apnea/Bradycardia Monitors
Ian Nathanson, MD; Jane O'Donnell, MSN; Mary F. Commins, BSN, Buffalo, NY

481 Use of Adrenergic Bronchodilators by Pediatric Allergists and Pulmonologists
Richard W. Newcomb, MD, Merrillville, Ind

SPORTS MEDICINE

486 High School Athletes and the Use of Ergogenic Aids
Daniel P. Krowchuk, MD; Trina M. Anglin, MD, PhD; Donald B. Goodfellow, MD; Terry Stancin, PhD; Paul Williams, MD; Gregory D. Zimet, PhD, Cleveland, Ohio

Continued on p 388.

The AMERICAN JOURNAL OF DISEASES OF CHILDREN is a member of the consortium of AMA journals listed below. The Archives reaches more than 41 500 readers in 85 countries each month. The complete text of all AMA journals is available on the MEDIS data base from Mead Data Central, Dayton, Ohio.

JAMA The Journal of the American Medical Association

AJDC American Journal of Diseases of Children

archives of **Dermatology**

archives of **General Psychiatry**

archives of **Internal Medicine**

archives of **Neurology**

archives of **Ophthalmology**

archives of **Otolaryngology-Head & Neck Surgery**

archives of **Pathology & Laboratory Medicine**

archives of **Surgery**

James H. Sammons, MD, Executive Vice-President

James S. Todd, MD, Senior Deputy Executive Vice-President

Kenneth E. Monroe, Deputy Executive Vice-President

Theodore R. Chilcoat, Jr, Assistant Executive Vice-President

M. Roy Schwarz, MD, Assistant Executive Vice-President

George D. Lundberg, MD, Vice-President, Scientific Information

John T. Baker, Vice-President, Publishing

Norman D. Richey, Director, Publication Production and Printing Division

Lee A. Parent, Director, Circulation-Fulfillment Division

Dennis Joseph Dennehy, Director, Advertising Sales and Promotion Services Division

Thomas J. Carroll, Director, Department of Advertising Communication

Raymond Christian, Director, Advertising Services Department

PUBLICATION STAFF
Offices: 535 N Dearborn St
Chicago, IL 60610

Managing Editor and Director, AMA Specialty Journals:
Michael D. Springer

Associate Editor:
Julie Foreman

Production Manager:
Marlene M. Hinsch

Assistant Production Manager:
John R. Sayban

Editorial Processing Manager:
Cheryl Iverson

Assistant Editorial Processing Manager:
Paula Glitman

Permissions and Graphic Design Manager:
Dennis J. Shipley

Staff Assistants:
Diane Darnell
Bonnie Van Cleven

Copy editing:
Patricia A. Predey (Supervisor)
Vickey Golden (Free-lance Coordinator)
Paul Frank (Senior Copy Editor)
Stephen Borysewicz
John Radanovich

Production Supervisors:
Betty Frigerio (Advertising)
Thomas J. Handrigan (Illustrations)
Elizabeth Petrikenas (Proofreading)
Mary C. Steermann (Editorial)
JoAnne Weiskopf (Layout)

Proofreading:
Teresa H. Omiotek
Richard T. Porter
Jennifer Reiling
Barbara Wojtowicz

Art and Senior Production Assistants:
Melinda Arcabos
Cari Biamonte
Laura Bleiler
Karen Branham
Cynthia Gelper
Jerri Hall-Gortowski
Anita Henderson
Debra Lucas
Kimberly McCormick
Juliana K. Mills
Dorothy Patterson
Susan Price
E. Ruth White
Ellen Yoshihara

Production Assistant:
Darlene E. Filips

Editorial Assistant:
Jean Schaffner

Department of Scientific and Socioeconomic Indexing:
Norman Frankel (Director)
George Kruto
Susan McClelland
Mary Kay Tinerella

Please address communications concerning accepted or published communications to AMA Specialty Journals, 535 N Dearborn St, Chicago, IL 60610.

EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

Continued from p 387.

ARTICLES

490 Measured Energy Expenditure in Pediatric Intensive Care Patients
Samuel J. Tilden, MD; Stephanie Watkins, RRT; Timothy K. Tong, MD; Malayappa Jeevanandam, PhD, Phoenix, Ariz

493 Frequency of Autoantibodies in Normal Children
Alberto Martini, MD; Renata Lorini, MD; Domenico Zanaboni; Angelo Ravelli, MD; Roberto G. Burgio, MD, Pavia, Italy

SPECIAL FEATURES

501 Picture of the Month
Brian J. Wiatrak, MD, Charles M. Myer III, MD (*Contributors*), Cincinnati, Ohio; Murray Feingold, MD (*Section Editor*), Brighton, Mass

503 Radiological Case of the Month
William A. Bonadio, MD (*Contributor*), Milwaukee, Wis; Beverly P. Wood, MD (*Section Editor*), Rochester, NY

BOOK REVIEW

Pediatric Medicine (Avery, First, eds) Reviewed by Jeffrey A. Wright, MD, Edgar K. Marcuse, MD, MPH, Seattle, Wash (p 464)

INSTRUCTIONS FOR AUTHORS (See February 1989 issue, p 136)

392 INDEX TO ADVERTISERS

AJDC, American Journal of Diseases of Children (ISSN 0002-922X) is published monthly by the American Medical Association, 535 N Dearborn St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

SUBSCRIPTION RATES—The subscription rates for the American Journal of Diseases of Children are as follows: $48 for one year, $81 for two years in the United States and US Possessions; all other countries, one year, $58; two years, $101 for surface delivery. (For expedited air delivery to most countries, add $15 surcharge for one year subscription, $30 for two years.) Rates for subscriptions for delivery to Japan or South Korea are available through exclusive agents—contact the publisher. ***Special rates for residents and medical students in the United States and US Possessions are available.*** Address inquries to the American Medical Association, Circulation and Fulfillment Division, 535 N Dearborn St, Chicago, IL 60610. Phone: (312) 280-7168.

CHANGE OF ADDRESS—POSTMASTER, send all address changes for AJDC, American Journal of Diseases of Children. Attention: Subscription Department, 535 N Dearborn St, Chicago, IL 60610. Notification of address change must be made at least six weeks in advance, include both old and new addresses, a recent mailing label, and your new zip code.

ADVERTISING OFFICES: Eastern: 600 Third Ave, Suite 3700, New York, NY 10016 (**Manager:** Robert C. Corcoran [212-867-6640]; **Representative:** Phillip B. Altamore); **Midwest/Farwest:** 535 N Dearborn St, Chicago, IL 60610 (**Manager:** Thomas J. Carroll [312-280-7182]; **Representative:** John P. Cahill, Midwest/Farwest)

Advertising Principles: Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.

Congratulations, Jackie...

Gold Medal Winner!

Lederle Biologicals is delighted to have sponsored Jackie DiLorenzo at the 1988 Paralympic Games in Seoul, Korea.

Overcoming stiff competition from the best wheelchair table tennis players in the world, Jackie brought home a Gold Medal!

This supreme accomplishment is the result of long-term dedication to her sport, combined with the determination to overcome the effects of poliomyelitis.

This dreaded disease struck Jackie before ORIMUNE became available, leaving her paralyzed from the waist down.

Like Jackie, Lederle Biologicals is fully dedicated to a long-term commitment: the protection of America's children from the ravages of polio.

Please see following page for brief summary of prescribing information.

Orimune®
Poliovirus Vaccine Live Oral Trivalent

Lederle Biologicals
® Protecting Families Through Immunization®

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

A Brief Summary

Please see package insert for full description, directions for use, and references.

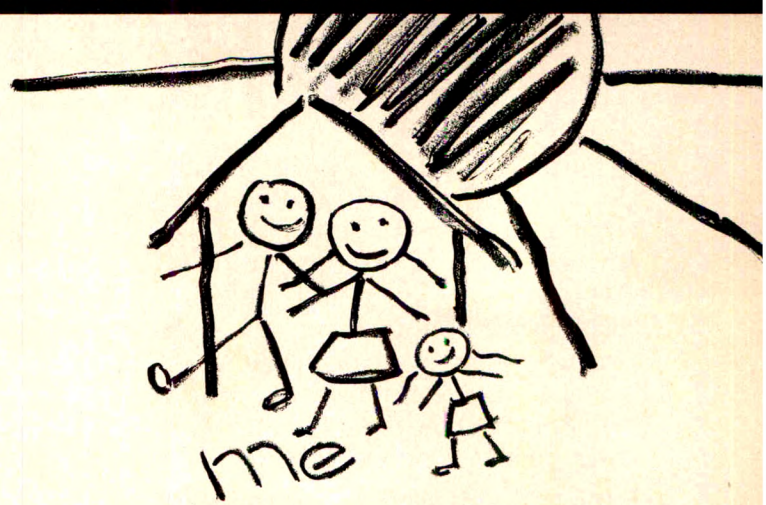
INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*
CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*
Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.
ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.
WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*
Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.
Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.
PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.
The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.
Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)
ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.
Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.
When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE®. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live poliovirus that had escaped inactivation.
The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."
The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev. 8/86

Lederle Biologicals
Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470. © 1989 Lederle Laboratories 181-9

SEX TALK FOR A SAFE CHILD



Child Safety
Everyone's concern

A unique coloring book that teaches children about their bodies AND about safety from abuse.

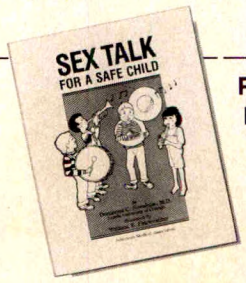
Features that make *Sex Talk for a Safe Child* a valuable book for children and adults:

- An interactive tool for adults to use with children.
- Teaches the difference between good loving relationships and dangerous ones.
- Illustrations are anatomically correct for clearer understanding.
- Children learn to "yell and tell" if they become victims of abuse.
- Coloring book format reinforces the concepts as children return to it in a play and learn setting.

Now you can purchase, at a reduced rate, a quantity of these newly revised and updated books to use with parents and children. Complete the order coupon below to obtain your copies of *Sex Talk for a Safe Child* today.

**** Special Offer***

Buy ten or more copies of *Sex Talk for a Safe Child* and you'll receive a free copy of the publication *AMA Diagnostic and Treatment Guidelines Concerning Child Abuse and Neglect.*

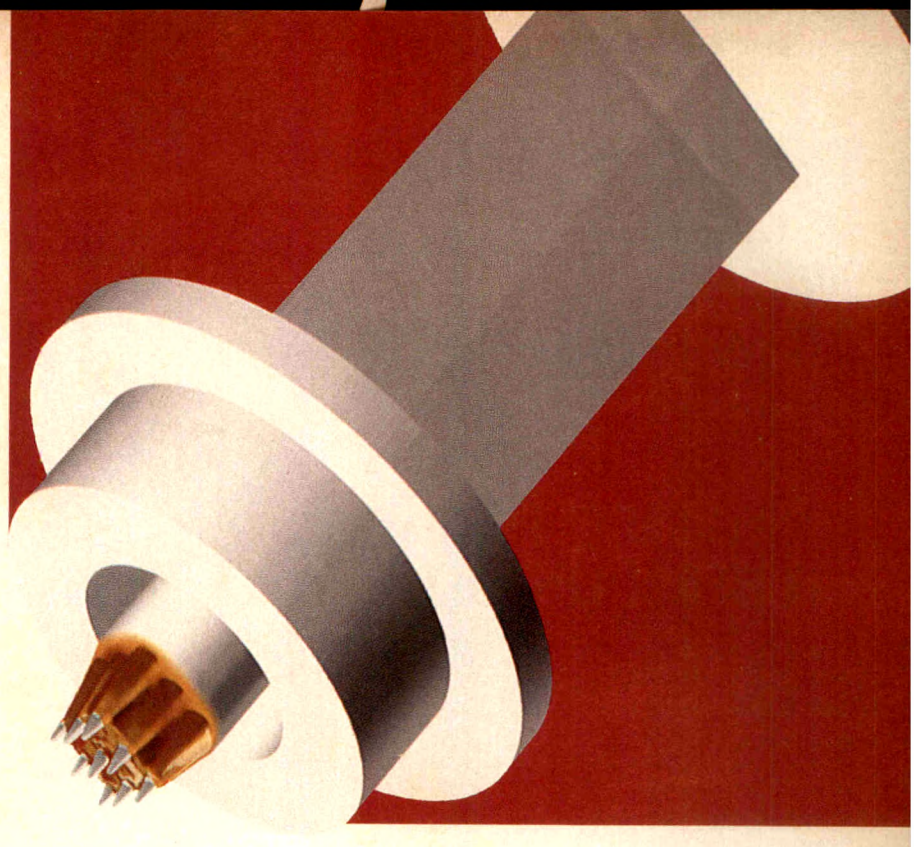


Please call 1-800-621-8335 to order using MasterCard or Visa. In Illinois call collect 312-645-4987. Or complete and mail to . . .
Book & Pamplet Fulfillment, OP-234/5.
American Medical Association
P.O. Box 10946
Chicago, IL 60610-0946

_____ 1 copy @ $5.00 $_____
_____ 5-9 copies @ $4.50 each $_____
_____ 10-24 copies @ $4.00 each $_____
_____ 25-49 copies @ $3.50 each $_____
Less 20% discount for AMA Members only $_____
Subtotal $_____
Plus appropriate Sales Tax for CA, DC, IL & NY $_____
TOTAL . . . . . $_____

- Payment must accompany order.
- Please allow 4 to 6 weeks for delivery.
- Prices subject to change without notice.
- Quantity discounts, call (312) 280-7168.

Name _____
Address _____
City _____
State _____ Zip _____
☐ Enclosed is my check payable to the American Medical Association
☐ MasterCard ☐ Visa
Card No. _____
Expiration Date _____ Phone No. _____
Cardholder's Signature _____



The symbol of accuracy and clarity in TB screening

Accuracy

98.8% agreement with Mantoux[1]

Co-positivity of MONO-VACC and MANTOUX test[1]

Study	N	Mantoux Positive	MONO-VACC Positive	Positive Agreement
STOCKER	1,406	279	274	**98.2%**
KRAVITZ, et al	1,959	87	87	**100.0%**
BYRD, et al	1,423	256	253	**98.8%**
GRABAU	2,022	60	60	**100.0%**
FREOUR, et al	443	195	188	**96.4%**
FURCOLOW, et al	670	258	254	**98.6%**
JENKINS, et al	84	80	84*	**100.0%**
TOTAL	8,007	1,215	1,200	**98.8%**

Adapted from Federal Register[1]

*Of these 84 bacteriologically-confirmed tuberculin patients, all 84 were correctly identified by MONO-VACC, while only 80 were considered by an FDA review panel to have had a positive reaction to Mantoux. The four "false negative" Mantoux responses (5-9 mm induration) would be considered positive by American Thoracic Society Standards.

†Tine Test and Aplitest are registered trademarks of Lederle Laboratories and Parke-Davis, respectively.

As with all screening tests, positive reactions should be confirmed by a standard Mantoux test.

Please see brief summary of product information on an adjacent page.

A reassuringly low rate of false negatives

A 1.6% incidence of false negatives (a 5.1% incidence of false positives)[2]–reportedly lower than Tine Test®† (O.T.) or Aplitest®† (PPD)[2]

Clarity

A single, easy-to-read reaction

MONO-VACC–the *only liquid* tuberculin screening test–is simple to administer, highly acceptable to patients, *and* easy to interpret.

MONO-VACC® TEST (O.T.) (TUBERCULIN, OLD)

To order MONO-VACC, call toll-free:
1-800-327-2842 Ext 113
(In Florida, call: 1-305-593-9577 Ext 113)

Distributed by
MERIEUX INSTITUTE, INC
Miami, FL 33126

Manufactured by
INSTITUT MÉRIEUX
Lyon–France
US Lic No. 384

© 1989, Merieux Institute, Inc

The symbol of accuracy and clarity in TB screening

MONO-VACC® TEST (O.T.) (TUBERCULIN, OLD)

(TUBERCULIN, OLD)
MONO-VACC® TEST (O.T.)

BRIEF SUMMARY

INDICATIONS
Screening for tuberculosis. Positive reactions should be confirmed by Mantoux method and possibly other diagnostic test procedures.

CONTRAINDICATIONS
None when test is used as directed.

WARNINGS
Although anaphylactic reactions have not been reported with Mono-Vacc, this remote possibility should be considered and epinephrine should be available.

PRECAUTIONS
Do not apply Mono-Vacc to acneiform skin, hairy areas or where there is inadequate subcutaneous tissue. Although repeated testing of uninfected individuals does not sensitize to tuberculin, it may have a "booster" effect in persons with low levels of sensitivity to homologous or heterologous mycobacterial antigens. Testing should be done with caution in persons with active tuberculosis, however, activation of quiescent lesions is rare. Tuberculin color variation may occur between different lots without alteration of potency or stability. Discard each Mono-Vacc test after use. DO NOT REUSE.

Drug Interactions:
The administration of adrenal corticosteroids or immunosupressive drugs may decrease the intensity of or prevent a tuberculin reaction. Tuberculin sensitivity may decrease or disappear temporarily as a result of febrile illness; measles and other exanthemas; live virus vaccination; sarcoidosis and miliary or pulmonary tuberculosis.

Pregnancy Category C. Tuberculin, Old:
Animal reproduction studies have not been conducted with Tuberculin, Old (Mono-Vacc Liquid Tuberculin Test, O.T.). It is also not known whether Tuberculin, Old can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Tuberculin, Old should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS
Vesiculation, ulceration, or necrosis may occur in highly sensitive subjects at the test site. Pain or pruritus at the test site may be relieved by topical glucocorticoid ointment or ice packs.

1/84

REFERENCES
1. Skin test antigens: Proposed implementation of efficacy review. *Federal Register* 1977;42 (September 30): 5207-5209.
2. Donaldson JC, Elliot RC: A study of co-positivity of three multipuncture techniques with intradermal PPD tuberculin. *Am Rev Respir Dis* 1978;118:843-846.

Distributed by
MERIEUX INSTITUTE, INC
Miami, FL 33126

Manufactured by
INSTITUT MÉRIEUX
Lyon-France
US Lic No. 384

INDEX TO ADVERTISERS

Allen & Hanburys, Division of Glaxo, Inc. 392A-D, 393
American Academy of Pediatrics 465
Aramco 440

Bionix Development Partnership 393

Carnation Company 386
Connaught Laboratories, Inc. 448A-D, 449

Fisons Corporation 445-446

Huntington Memorial Hospital 440

ICN Pharmaceuticals, Inc. 464A-D

Lederle Laboratories 389-390, 505-506

McNeil Consumer Products Company .....394, Cover 3
Merieux Institute, Inc. 391-392

National Biological Corporation 440
National Institutes of Health 393

Osler Institute 508

A.H. Robins Company .....Cover 2
Rorer Pharmaceuticals 499-500

Sandoz Pharmaceuticals 450, 497-498

Wyeth-Ayerst Laboratories .....Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

ALCOHOL IS NOT FOR UNBORN BABIES

Having a baby is a time to take special care of yourself. When you're pregnant, everything you eat and drink affects the child you are carrying.

Drinking beer, wine or liquor may hurt your baby. Heavy drinking can result in serious permanent mental and physical birth defects.

Alcohol is not something to be taken lightly during pregnancy. For baby's sake... and yours... the safest choice is not to drink during pregnancy.

For more information, write the National Clearinghouse for Alcohol Information, Box 2345, Rockville, MD 20852.

NIAAA NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

CONGENITAL ADRENAL HYPERPLASIA REFERRAL

The Clinical Center requests the cooperation of physicians in the referral of growing children with congenital adrenal hyperplasia for a study on the relative effectiveness of once-daily compared to twice-daily hydrocortisone administration. The bone age must be ≤ 11 years for boys and ≤ 9 years for girls.

Patients will be followed in conjunction with their referring physicians over the 2-year duration of the study. At the completion of the study patients will be returned to the care of their referring physician. Please write or telephone:

Dr. Louisa Laue or
Dr. Gordon B. Cutler, Jr.
Building 10, Room 10N-262
National Institutes of Health
Bethesda, Maryland 20892
Tel: (301) 496-4686

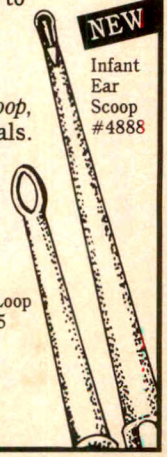
HERE'S THE SCOOP

A safer, more effective method of ear curettage. Both the *Flex-Loop* and the *Infant Ear Scoop* are designed to quickly and easily remove cerumen while avoiding trauma to the ear canal. The low cost makes them easily affordable and their single use disposability eliminates the risk of contamination.

The *Flex-Loop* flexible ear curette is made of virtually unbreakable polypropylene, allowing the loop to flex to conform to ear anatomy – particularly valuable in a wiggling child. Yet the *Flex-Loop* is stiff enough to remove most types of cerumen quickly and easily, allowing a clear view for accurate evaluation of the tympanic membrane.

Newly available is the smaller *Infant Ear Scoop*, specially designed for the tiniest of ear canals. Its 2 mm width was created in response to physician demand, with a spoon-like design that provides effective removal of cerumen, and a tear-drop shape that allows safe and comfortable curettage of the infant ear.

NEW
Infant Ear Scoop #4888



Flex-Loop #9555

To order or for more information call **1-800-541-5069**

Bionix Development Partners
757 Warehouse Rd.
Suite G
Toledo, OH 43615

BIONIX

"OUCH"

For "minor league" injuries, there's a better choice than aspirin

When your 6- to 14-year-old patients need pain relief for minor injuries, Junior Strength TYLENOL® acetaminophen should be your first choice. Clinical studies have proven TYLENOL® to be every bit as effective as aspirin for pain relief,[1] with a superior safety profile.[2] Together with the recommended regimen of rest, ice, compression, and elevation, it's the better choice than aspirin for the pain of minor self-limiting injuries.[3]

Junior Strength TYLENOL® can also help reduce underdosing because children need only half as many 160 mg caplets as 80 mg chewables. They're coated for easier swallowing, too.

So next time a junior patient says "Ouch!", recommend local therapy for the inflammation, and make your first choice Junior Strength TYLENOL® acetaminophen for the pain.

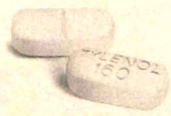
References: 1. Cooper SA: *Arch Intern Med* 1981;141:282–285. **2.** Aspirin or paracetamol? *Lancet* 1981;II:287–289. **3.** Senior RJ: *J Adolesc Health Care* 1986;7(suppl to No. 6):24S–30S.

JUNIOR STRENGTH

TYLENOL®

160 mg acetaminophen

COATED CAPLETS



First choice for pain relief in the 6–14 year old

© McN, 1988

McNeil Consumer Products Company
Fort Washington, PA 19034

McNEIL

AMBULATORY PEDIATRIC ASSOCIATION

Program and Abstracts

TWENTY-NINTH ANNUAL MEETING

MAY 1-5, 1989

SHERATON HOTEL

WASHINGTON, DC

All of the material received from the Ambulatory Pediatric Association, including the abstracts, has been printed as received without copyediting by the staff at AJDC *or the AMA. The AMA,* AJDC, *and the Editor are not responsible for any errors in content, style, grammar, or spelling.*

APA APPLICATION FOR MEMBERSHIP

Information for Prospective Members

The objectives of the Ambulatory Pediatric Association are to improve the teaching of general pediatrics, to improve research in general pediatrics, to improve patient services in general pediatrics, and to affect public and governmental opinion regarding issues vital to teaching and research in general pediatrics. Applications for membership will be considered from members of the health care professions involved in teaching and patient care or research in general pediatrics.

Application forms are obtained from the Executive Secretary's Office:

Executive Secretary
Ambulatory Pediatric Association
6728 Old McLean Village
McLean, VA 22101
(703) 556-9222

Future Annual Meetings

1990—May 7-11, Hilton Hotel, Anaheim, Calif
1991—April 29-May 3, Riverside Hilton, New Orleans, La
1992—May 4-8, Baltimore Convention Center, Baltimore, Md
1993—May 3-7, Sheraton Hotel, Washington, DC

APA PROGRAM SCHEDULE

Date and Time	Event	Room
Monday, May 1		
7 PM-10 PM	APA Board of Directors' Meeting	Colorado
Tuesday, May 2		
7:30 AM-Noon	APA Board of Directors' Meeting	Colorado
8 AM-9 AM	St Geme Award	Sheraton Ballroom
1:30 PM-4:30 PM	APA Workshops 1-10	See Page 401
	APA Special Interest Groups	
	Emergency Medicine	Holmes
	Day Care Issues	Calvert
	Nurse Practitioners	Woodley
	Behavioral Pediatrics	Colorado
	RWJ Clinical Scholars General Pediatrics Alumni	Johnson
	Childhood Nutrition/ Disease Prevention	Lanai 156
5 PM-7 PM	APA Committee Meetings	
	Research	Lanai 144
	Education	Woodley
	Child Health Care Delivery	Calvert
	Public Policy	Idaho
	Publications	Lanai 148
	Serving the Underserved	Lanai 152
	VLBW	Colorado
Wednesday, May 3		
7:30 AM-9 AM	APA Past Officers' Breakfast	Holmes
9 AM-Noon	APA Topic Sessions	
	Adolescent Medicine and Pediatric Education	Dover
	Develop-mental and Behavioral Pediatrics	Virginia Suite
	Clinical Issues	Wilmington
	Emergency Pediatrics and Child Abuse	Baltimore/ Annapolis
	Prevention and Epidemiology	Rockville
1:30 PM-4:30 PM	APA Workshops 11-20	See Page 401
	APA Special Interest Groups	
	Clerkship Directors (Starts at 12:30 PM)	Rockville
	Child Abuse	Johnson
	HMO	Colorado
	Injury Control	Holmes
	Adolescence	Kennedy
5:15 PM-6:30 PM	APA Teaching Award	
	APA Business Meeting	Virginia Suite
8:15 PM-9:45 PM	APA Debate	Maryland Suite
Thursday, May 4		
7:30 AM-9 AM	APA Regional Breakfast Meetings	
	Region I	Ethan Allen
	II	Embassy
	III	Thomas Paine
	IV	Kansas
	V	Nathan Hale
	VI	Lanai 144
	VII	Idaho
	VIII	Lanai 148
	IX	Wisconsin
	X	Colorado

APA PROGRAM SCHEDULE (con't)

Date and Time	Event	Room
9:30 AM-12:30 PM	APA Workshops 21-30	See Page 402
	APA Special Interest Groups	
	Chronic Illness	Marshall
	Homeless Children	Woodley
	Practice Management	Holmes
	Primary Care Grants	Calvert
	International Health	Warren
12:30 PM-2 PM	APA Special Interest Group Chairs' Luncheon	Thomas Paine
	APA Regional Chairs' Luncheon	Ethan Allen
2 PM-5:30 PM	Joint Topic Sessions With American Pediatric Society and Society for Pediatric Research	
	Adolescent Medicine	Washington Ballroom
	Behavioral Pediatrics	Delaware Suite
	Epidemiology and Preventive Pediatrics	Virginia Suite
	General Pediatrics and Pediatric Education	Maryland Suite
5:45 PM-6:45 PM	APA Armstrong Award	Washington Ballroom
6:45 PM-7:45 PM	APA Reception	Delaware Suite
Friday, May 5		
8:15 AM-Noon	General Plenary Session and President's Address	Virginia Suite
1:15 PM-5 PM	APA Board of Directors' Meeting	Nathan Hale

REGISTRATION HOURS

Convention Registration A&B — Lobby Level

Monday, May 1	Noon-9 PM
Tuesday, May 2	7:30 AM-8 PM
Wednesday, May 3	7:30 AM-5 PM
Thursday, May 4	7:30 AM-5 PM
Friday, May 5	7:30 AM-Noon

Workshop Registration

Tuesday, May 2	7:30 AM-8 PM
Wednesday, May 3	7:30 AM-8 PM
Thursday, May 4	7:30 AM-Noon

This meeting is being accredited by the American Academy of Pediatrics, Elk Grove Village, Ill. This program meets the criteria for 53 category 1 hours of the Physician's Recognition Award of the American Medical Association and of the Pediatrics Review and Education Program (PREP).

The California State Board of Registered Nursing has approved this program for 22¾ Continuing Education Credits for Registered Nurses. Certificates will be available at the APA registration desk.

AMBULATORY PEDIATRIC ASSOCIATION

1988-1989

Officers

President ..... Steven P. Shelov, MD, New York, NY
President-Elect ..... Paul McCarthy, MD, New Haven, Conn
Secretary-Treasurer ..... Kathleen Nelson, MD, Birmingham, Ala
Newsletter Editor ..... Lindsey K. Grossman, MD, Columbus, Ohio
Immediate Past President ..... Ruth E. K. Stein, MD, New York, NY

Board of Directors

Carol Berkowitz, MD ..... Torrance, Calif
Thomas DeWitt, MD ..... Worcester, Mass
Larrie Greenberg, MD ..... Washington, DC
Robert H. Pantell, MD ..... San Francisco, Calif
Frederick P. Rivara, MD ..... Seattle, Wash
Modena E. H. Wilson, MD ..... Baltimore, Md

Regional Chairs

I. William Bithoney, MD ..... Boston, Mass
II. William M. Schwartz, MD ..... Philadelphia, Pa
III. Howard R. Foye, Jr, MD ..... Rochester, NY
Kenneth M. McConnochie, MD ..... Rochester, NY
IV. Michael Sharp, MD ..... Chapel Hill, NC
V. Sheldon L. Brenner, D.O. ..... Detroit
VI. Jerold Woodhead, MD ..... Iowa City, Iowa
VII. Rebecca Kirkland, MD ..... Houston, Tex
VIII. Joseph Pesek, MD ..... Jacksonville, Fla
IX. Sandra L. Elvik ..... Torrance, Calif
Rickey Williams, MD ..... Tucson, Ariz
X. Kathi Kemper, MD ..... Seattle, Wash

Past Presidents

1961-62 Richard W. Olmsted
1962-63 Morris Green
1963-64 Robert J. Haggerty
1964-65 Frederic M. Blodgett
1965-66 Donal Dunphy
1966-67 Loren G. MacKinney
1967-68 Lewis M. Fraad
1968-69 Hugo Dunlap Smith
1969-70 Joel J. Alpert
1970-71 John H. Kennell
1971-72 Donald Fink
1972-73 Ray E. Helfer
1973-74 Katherine S. Lobach
1974-75 Evan Charney
1975-76 Frederick North, Jr
1976-77 Margaret C. Heagarty
1977-78 Robert Hoekelman
1978-79 George Comerci
1979-80 Ivan Barry Pless
1980-81 Barbara Starfield
1981-82 Alvin Novack
1982-83 Philip Nader
1983-84 Fredric D. Burg
1984-85 Abraham B. Bergman
1985-86 Catherine DeAngelis
1986-87 Jay E. Berkelhamer
1987-88 Ruth E. K. Stein

Past Secretary-Treasurers

1961-1963 Frederic M. Blodgett
1963-1966 Hugo Dunlap Smith
1966-1969 Abraham B. Bergman
1969-1972 Katherine S. Lobach
1972-1974 Elizabeth S. Hillman
1974-1977 George Comerci
1977-1980 Fredric D. Burg
1980-1983 Barbara Durand
1983-1986 Marie McCormick

THE GEORGE ARMSTRONG LECTURE

George Armstrong, an English physician of the 18th century, established the first dispensary for children in London, England, in 1769. There he served with great devotion and taught others the care of sick children. He is honored as one of the fathers of modern pediatrics, and those who deliver this lecture are also honored as outstanding teachers and contributors to our knowledge of the care of children.

The lecture is sponsored by Ross Laboratories, Columbus, Ohio.

1967 George A. Silver
1968 Allan M. Butler
1969 Robert H. Haggerty
1970 Julius B. Richmond
1971 Morris Green
1972 Henry K. Silver
1973 Barbara M. Korsch
1974 Lewis Fraad
1975 C. Henry Kempe
1976 Abraham B. Bergman
1977 Wilbur J. Cohen
1978 Richard W. Olmstead
1979 John H. Kennell
1980 OXFAM (Tim Lusty)
1981 Benjamin Spock
1982 Evan Charney
1983 Barbara Starfield
1984 Victor Vaughan
Waldo Nelson
1985 Gerold L. Schiebler
1986 Marian Wright Edelman
(Children's Defense Fund)
1987 Robert A. Hoekelman
1988 Ivan Barry Pless
1989 Joel J. Alpert

APA TEACHING AWARD

The purpose of this award is to foster interest in the teaching of ambulatory pediatrics by giving national recognition to an outstanding ambulatory pediatric program. Programs must demonstrate excellence in educational teaching methods, acceptance by students and/or residents, acceptance by the community and the institution, innovations and adaptability, or outstanding quality of the individuals trained in the program. Emphasis is placed on the award being given to *an* outstanding *program*.

1972 University of Arizona
College of Medicine
Department of Pediatrics
Division of Ambulatory
Pediatrics
Tucson
1976 University of Chicago
Pritzker School of Medicine
Wyler Children's Hospital
Division of Ambulatory
Pediatrics
1977 University of Vermont
College of Medicine
Department of Pediatrics
Division of Ambulatory
Pediatrics
Burlington, Vt
1978 Children's Hospital of
Philadelphia
Division of Ambulatory
Services
Resident Group Practice
1980 Primary Care Training
Program
Department of Pediatrics
University of Arizona
College of Medicine
Tucson
1981 Sinai Hospital of Baltimore
Pediatric Residency Training
Program
1982 Child Health Associate
Program
University of Colorado
Health Sciences Center
Denver
1984 University of North
Carolina—Chapel Hill
Department of Pediatrics
Community Outreach
Training Program
1986 Pediatric Practice Model
University of Oklahoma
College of Medicine
Oklahoma City
1987 Chronic Illness Teaching
Program
Department of Pediatrics and
Human Development
Michigan State University
East Lansing
1988 Emergency Room Teaching
Program
Children's Hospital of
Philadelphia (Pa)
and
Behavioral and
Developmental
Pediatric
Fellowship
Program
Ohio State University
Department of Pediatrics
Columbus
1989 Primary Care Training
Program
University of California—
San Diego Department of
Pediatrics
Division of General Pediatrics

APA WORKSHOPS

Tuesday, May 2, 1989

SESSION I

1:30 PM-4:30 PM

1. **The General Physical Exam of a Journal Article** ..... Taft
   Leaders: T. Mc.Jones, R. A. Etzel, and C. A. Kozinetz
2. **Teaching Skills for Community Preceptors: A Faculty Development Model** ..... Wisconsin
   Leaders: T. G. DeWitt, R. L. Goldberg, and D. P. Briggs
3. **Making Your Clinic 'User-Friendly' for Practice, Teaching and Research** ..... Idaho
   Leaders: P. G. Szilagyi, L. E. Rodewald, K. M. McConnochie, and K. J. Roghmann
4. **Establishment of a Regionalized Referral Center for Comprehensive Health Planning for Children With Chronic Illness** ..... Eisenhower
   Leaders: W. McCoy, A. Diano, J. Lipman, R. Halper, and R. E. K. Stein
5. **The Pediatric Clerkship Director: Juggling Responsibilities and Surviving Academia** ..... Roosevelt
   Leaders: L. W. Greenberg and O. J. Z. Sahler
6. **How to Develop a Course on Enhancing Presentation Skills** ..... Lanai 144
   Leaders: D. M. Super, R. E. Marshall, and J. Cullen
7. **Pediatric Environmental Hazards: A Tip-Toe Through the Toxins** ..... Truman
   Leaders: J. L. Mayer and S. J. Balk
8. **Teaching Bedside Teaching Skills** ..... Warren
   Leaders: R. T. Sarkin, S. Lazoritz, and J. J. Roetter
9. **Community-Wide Approaches to Promoting the Health and Development of Families and Young Children** ..... Kennedy
   Leaders: R. W. Chamberlin and S. Bauer
10. **Capitation and the Pediatrician** ..... Kansas
    Leaders: G. B. Hickson and J. T. Badgett

APA WORKSHOPS

Wednesday, May 3, 1989

SESSION II

1:30 PM-4:30 PM

11. **Teaching Technical Skills in Pediatrics: Current Concepts** ..... Warren
    Leaders: S. Selbst, L. Bell, M. D. Baker, K. Shaw, K. Cronan, and J. Wiley
12. **Training Residents to Convey Distressful Information** ..... Truman
    Leaders: M. L. Wolraich and M. L. Drymon
13. **Keeping Bias at Bay: The Art and Science of Sample Selection for Research Cases and Controls** ..... Woodley
    Leaders: APA Research Committee
14. **Research Funding for Primary Care Health Services and Behavioral Pediatrics** ..... Calvert
    Leaders: K. Kelleher and J. Mayfield
15. **Child Development, Pain and Mental Imagery** ..... Roosevelt
    Leaders: R. Solomon and C. Saylor
16. **Infant Daycare and Maternal Employment: Implications for Pediatrics** ..... Wisconsin
    Leaders: H. Dubowitz, K. L. Kotloff, and D. M. Teti
17. **School Health Training for Pediatric Residents: The Whys and the Hows** ..... Idaho
    Leaders: V. Niebuhr and D. McCormick
18. **Infection, Violence, and Exposure in Acute Care: Reducing Personal Risk** ..... Taft
    Leaders: L. Bell, S. Selbst, F. Henretig, J. Avner, K. Cronan, and L. Pachter
19. **Design of Computer Instruction Media Using Hypercard** ..... Kansas
    Leader: W. Schwartz
20. **Child Health Advocacy: How to Do It/Can We Teach It?** ..... Eisenhower
    Leader: W. S. Davis

APA WORKSHOPS

Thursday, May 4, 1989

SESSION III

9:30 AM-12:30 PM

21. **Sedation and Analgesia in the Outpatient Setting** ..... Wisconsin
Leaders: Emergency Medicine Interest Group (A. B. Anderson, S. Asch, M. Baskin, E. Crain, D. Hodge, D. Jaffe, J. Knapp, D. Lubitz, S. Selbst, and S. Torrey)
22. **Ingestion Management: Routines Revisited and Dogma Disputed** ..... Roosevelt
Leaders: E. F. Crain, J. C. Gershel, I. Kaufman, M. Sonnett, and A. P. Mezey
23. **Sports Medicine for the Pediatrician** ..... Kansas
Leader: G. L. Landry
24. **A Comprehensive Approach to Infants of Substance Abusing Mothers** ..... Eisenhower
Leaders: C. Berkowitz and S. Elvik
25. **Regionalizing Care for Critically Ill and Injured Children: Coast to Coast Experience** ..... Kennedy
Leaders: G. Foltin, M. Tunik, A. Cooper, J. Seidel, D. Henderson, E. van der Jagt, R. Luten, L. Quan, and D. Brownstein
26. **The Awkward Age: Aspects of Injury in 5 to 14 Year Olds** ..... Idaho
Leaders: APA Injury Group
27. **Behavioral and Family-Based Intervention for Childhood Obesity** ..... Truman
Leaders: L. D. Hammer and J. L. Zimmerman
28. **Substance Abuse: Individual and Family Effects (What the Pediatrician Should Know and Can Do)** ..... Johnson
Leaders: H. Adger, E. M. McDonald, R. K. White, and A. K. Duggan
29. **The Pediatrician's Role in Trauma Management** ..... Taft
Leaders: S. Ludwig, M. D. Baker, C. Briede, J. Lavelle, T. Woodward, and B. King
30. **Sample Size Estimation for Clinical Research** ..... Colorado
Leader: Thomas B. Newman

APA TOPIC SESSIONS

Wednesday, May 3, 1989

9 AM-Noon

ADOLESCENT MEDICINE AND PEDIATRIC EDUCATION

Dover

Moderators: Larrie Greenberg, MD, and O. J. Sahler, MD

9:00 **Anabolic Steroids and High School Students.** L. G. McLain. Department of Pediatrics, Loyola University Stritch School of Medicine, Maywood, Ill.

9:15 **Pediatricians' Views of Appropriate Access to Care for Adolescents.** G. V. Fleming, K. G. O'Connor, and J. M. Sanders. Department of Research, American Academy of Pediatrics, Elk Grove Village, Ill.

9:30 **Risk Factors for C. Trachomatis Cervical Infection in Adolescent Females.** M. K. Oh, R. A. Feinstein, E. J. Soileau, G. Cloud, and R. F. Pass. Department of Pediatrics, Division of Adolescent Medicine, Division of Infectious Disease, University of Alabama, Birmingham.

9:45 **Adolescents Who Smoke 'Crack': Patterns and Consequences of Use.** R. H. Schwartz, N. G. Hoffman, and M. Luxemburg. Department of Pediatrics, Fairfax (Va) Hospital, STRAIGHT Inc, Springfield, Va, and CATOR, St Paul, Minn.

10:00 **Rehabilitation of Chemically Dependent Adolescents: A Follow-up Survey.** D. E. Smith, R. H. Schwartz, and M. E. Gutgesell. Department of Pediatrics, University of Virginia Health Sciences Center, Charlottesville.

10:15 **Percentage Body Fat Determinations in 4,360 Adolescent Athletes.** B. A. Spear and R. A. Feinstein. Department of Pediatrics, University of Alabama, Birmingham.

10:30 **Safer Sex and Adolescent Condom Use.** A. Joffe, S. M. Radius, and M. Gall. Department of Pediatrics, Johns Hopkins Medical Institutions, Baltimore, Md.

10:45 **Teaching About Sexuality and AIDS: A Comparison of Health Professionals and Peer Educators.** D. M. Siegel, J. Neuderfer, W. H. Zimmerli, and D. Gilson. Department of Pediatrics, Rochester General Hospital, University of Rochester (NY).

11:00 **Does Systematic Feedback Improve Clinical Teaching?** T. R. Schum, K. J. Yindra, R. G. Koss, and D. B. Nelson. Department of Pediatrics, Medical College of Wisconsin, Milwaukee.

11:15 **Measured Outcome of a New Curriculum Varies Among Residents, Simulated Mothers, and Blind Coders.** D. Kittredge, R. Olson, P. Buck, and A. Cucchiara. Departments of Pediatrics, Psychiatry and Behavioral Sciences, and Bio-Statistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City.

11:30 **How Do General Pediatric Clinics Function From the Perspective of the Practice Manager? Results of a Survey of Academic Departments.** J. E. Berkelhamer. Department of Pediatrics, University of Chicago Pritzker School of Medicine, Wyler Children's Hospital, Chicago, Ill.

11:45 **Pregnancy During Pediatric Residency: Attitudes and Complications.** J. Klevan, J. Weiss, and S. Dabrow. Department of Pediatrics, Thomas Jefferson University, Philadelphia, Pa.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Virginia Suite

Moderators: Kathleen Nelson, MD, and Lindsey Grossman, MD

9:00 **Academic Achievement and Its Correlates in a Community Sample of Chronically Ill Children.** M. C. Starr and F. C. Jarman. Department of Pediatrics, University of Massachusetts Medical School, Worcester.

9:15 **The Effect of Mother's Health on the Care of a Chronically Ill Child.** J. L. Lauby, L. J. Bauman, and R. E. K. Stein. Department of Pediatrics, Preventive Intervention Research Center for Child Health, Albert Einstein College of Medicine, Bronx, NY.

9:30 **'Unrecognized' Chronically Ill Children in School: A Group at Risk for Psychosocial Difficulties.** F. C. Jarman and M. C. Starr. Department of Pediatrics, University of Massachusetts Medical School, Worcester.

9:45 **The Relationship Between Knowledge and Behavior in Childhood Asthma.** J. L. Lauby, D. H. Rubin, and L. J. Bauman. Department of Pediatrics, Preventive Intervention Research Center for Child Health and Division of Pediatric and Perinatal Epidemiology, Albert Einstein College of Medicine, Bronx, NY.

10:00 **The Value of the Einstein Assessment of School-Related Skills in a Pediatric Clinical Setting.** R. L. Gottesman and F. M. Cerullo. Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY.

10:15 **Neurodevelopmental Assessment of Urban, Disadvantaged Second Graders Using the Pediatric Early Elementary Examination.** L. S. Grossman, M. M. Kappelman, T. Kenny, and R. G. Chernoff. Department of Pediatrics, University of Maryland School of Medicine, Baltimore.

10:30 **Preschool Neurodevelopmental Testing and Reading Outcome in Grades 2 and 3.** J. B. Chessare, D. Zinna, J. Joost, C. Liebich, and M. Weaver. Department of Pediatrics, The Medical College of Ohio, Toledo.

10:45 **Identifying Positive Attributes in Children With Attention Deficits.** D. P. Kelly, M. D. Levine, and M. R. Burchinal. Clinical Center for the Study of Development and Learning, University of North Carolina School of Medicine, Chapel Hill.

11:00 **Sexual Abuse: Factors Influencing Custody Decisions.** P. K. Jaudes and M. Morris. La Rabida Children's Hospital and Research Center (LRCH), Department of Pediatrics, University of Chicago (Ill).

11:15 **Effects of Early Carrying of Premature Infants on Cognitive Development.** D. Wagner, E. Anisfeld, and N. Cunningham. Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY.

11:30 **The Effects of Social Support on the Parturition of Primigravidous Mothers.** J. M. Pascoe. Department of Pediatrics, University of Wisconsin, Madison.

11:45 **The Use of a Perinatal Risk Inventory to Predict Developmental Outcome in the High Risk Neonates.** A. P. Scheiner. Department of Pediatrics, University of Massachusetts Medical Center, Worcester.

CLINICAL ISSUES

Wilmington

Moderators: Thomas DeWitt, MD, and Modena Wilson, MD

9:00 **Influence of β-Lactamase–Producing Flora on Recovery of Group A Streptococci Following Treatment of Acute Pharyngitis.** R. R. Tanz, S. T. Shulman, P. A. Sroka, and R. Yogev. Department of Pediatrics, Children's Memorial Hospital, Northwestern University, Chicago, Ill.

9:15 **Evaluation of the Efficacy of Topical Mupirocin Vs Oral Erythromycin for Treatment of Impetigo.** L. L. Barton, A. D. Friedman, A. M. Sharkey, D. J. Schneller, and E. M. Swierkosz. Department of Pediatrics, St Louis (Mo) University School of Medicine.

9:30 **The Influence of Footwear Upon Childhood Injury.** M. D. Baker and R. E. Bell. Department of Emergency Medicine, Children's Hospital of Philadelphia (Pa).

9:45 **Lack of Efficacy of an Antihistamine-Decongestant Combination in Resolving Systemic Symptoms Associated With Acute Suppurative Otitis Media.** J. M. Devries and R. A. Hoekelman. Departments of Pediatrics, Henry Ford Hospital, Detroit, Mich, and University of Rochester (NY) Medical Center.

10:00 **Twice-Daily Antibiotics for Acute Otitis Media (AOM) in Children: TMP-SMZ Vs Amoxicillin-Clavulanate (Amox-Clav).** W. Feldman, T. Sutcliffe, and C. Dulberg. Department of Pediatrics, The Children's Hospital of Eastern Ontario, and Epidemiology, University of Ottawa (Canada).

10:15 **Do Anemic Infants on Iron-Fortified Formula Need More Iron?** M. Irigoyen, L. L. Davidson, and C. Seaman. Department of Pediatrics, Columbia University, New York, NY.

10:30 **Diagnostic Efficacy of the Peripheral Blood Immature-to-Total Neutrophil Ratio for Bacterial Meningitis in Children.** R. Lembo, D. Rubin, D. Krowchuk, and P. McCarthy. Departments of Pediatrics, Yale University, New Haven, Conn, and Case Western Reserve University at Cleveland (Ohio) Metropolitan General Hospital.

10:45 **Pseudomonas in Pediatric Patients With Appendicitis.** I. Kaufman, G. Weinberg, J. Glaser, and E. Crain. Departments of Pediatrics and Surgery, Albert Einstein College of Medicine, Bronx, NY.

11:00 **Laboratory Investigation of Jaundiced Newborns: Frequency, Cost, and Yield.** T. B. Newman, M. J. Easterling, E. S. Goldman, and D. K. Stevenson. Departments of Pediatrics, Epidemiology, and Laboratory Medicine, University of California, San Francisco.

11:15 **Multivariate Predictive Model for Bacterial Meningitis in Febrile Children.** R. Lembo, D. Rubin, D. Krowchuk, and P. McCarthy. Departments of Pediatrics, Yale University, New Haven, Conn, and Case Western Reserve University at Cleveland (Ohio) Metropolitan General Hospital.

11:30 **In Utero Exposure to Cocaine: The Risk of SIDS.** H. Bauchner, B. Zuckerman, M. McClain, D. Frank, L. Fried, and H. Kayne. Division of Developmental and Behavioral Pediatrics, Boston (Mass) City Hospital.

11:45 **Who Takes Care of the Sickest Children?** M. Irigoyen and M. Goldstein. Department of Pediatrics, Columbia University, New York, NY.

EMERGENCY PEDIATRICS AND CHILD ABUSE

Baltimore/Annapolis

Moderators: Carol Berkowitz, MD, and Ellen Crain, MD

9:00 **Legal Proof of Child Sexual Abuse in the Absence of Physical Evidence.** A. R. De Jong and M. Rose. Department of Pediatrics, Thomas Jefferson University, Philadelphia, Pa, Philadelphia District Attorney's Office.

9:15 **Accuracy of Assessment in Child Sexual Abuse.** R. M. Brayden, W. A. Altemeier III, P. Siegel, and P. M. Speck. Department of Pediatrics, Vanderbilt University, Nashville, Tenn, and Memphis (Tenn) Rape Crisis Center.

9:30 **Is Childhood Sexual Abuse (CSA) Really Increasing in Prevalence? An Analysis of the Evidence.** W. Feldman, E. Feldman, J. Goodman, P. McGrath, R. Pless, L. Corsini, and S. Bennett. Departments of Pediatrics, Psychology, and Social Services, Children's Hospital of Eastern Ontario, Ottawa, Canada.

9:45 **Depth to Obtain a Clear Lumbar Puncture in Children Under 2 Years of Age.** L. D. Kaye, D. Suskin, and D. M. Super. Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio.

10:00 **Abbreviated Cerebrospinal Fluid Analysis in Selected Pediatric Patients.** L. E. Rodewald, K. A. Woodin, P. G. Szilagyi, D. A. Arvan, and K. R. Powell. Departments of Pediatrics, Pathology, and Laboratory Medicine, University of Rochester (NY), School of Medicine and Dentistry.

10:15 **Reliability of Physical Signs of Meningitis in Children With Meningitis.** M. P. Donahue and N. A. Schonfeld. Department of Emergency Medicine, Children's Hospital of Los Angeles (Calif).

10:30 **Prediction of Bacteremia Based on Temperature and WBC.** D. Jaffe and G. Fleisher. Children's Memorial Hospital, Northwestern University Medical School, Chicago, Ill, and The Children's Hospital, Harvard University Medical School, Boston, Mass.

10:45 **Hyperpyrexia in Childhood: A Case Controlled Study.** G. Alpert, E. Hibbert, and G. R. Fleisher. Department of Emergency Medicine, Children's Hospital, Boston, Mass.

11:00 **Radial Head Subluxations.** J. E. Schunk. Division of Emergency Medicine, Children's Hospital of Los Angeles (Calif).

11:15 **Selecting Extremity Injuries for X-ray: New Method for Protocol Development.** K. M. McConnochie and K. J. Roghmann. Department of Pediatrics, Rochester General Hospital, University of Rochester (NY).

11:30 **Acute Iron Poisonings in Children: Evaluation of the Predictive Value of Clinical and Laboratory Parameters.** N. A. Schonfeld and A. J. Haftel. Division of Emergency Medicine, Children's Hospital of Los Angeles (Calif).

11:45 **Indigent Patients Who Are Denied Care in the Emergency Departments.** K. N. Shaw, S. M. Selbst, and F. M. Gill. Emergency Department, Children's Hospital of Philadelphia (Pa).

PREVENTION AND EPIDEMIOLOGY

Rockville

Moderators: Robert Pantell, MD, and
Ruth E. K. Stein, MD

9:00 **Reducing Illness in Child Care Centers.** C. Lewis, C. Gilliss, R. Pantell, and B. Holaday. Department of Pediatrics, University of California, San Francisco.

9:15 **Reduction of Infectious Disease Symptoms in Day Care Homes.** A. Butz, P. Fosarelli, and E. Larson. School of Nursing and Department of Pediatrics, School of Medicine, Johns Hopkins University, Baltimore, Md.

9:30 **Bullets, BBs, and Boys: Understanding Gun Injuries Treated at a Pediatric Trauma Center.** R. R. Tanz and M. J. Barthel. Departments of Pediatrics and Pediatric Surgery, Children's Memorial Hospital, Northwestern University, Chicago, Ill.

9:45 **Attributing Cause for Unnecessary Pediatric Hospital Days Using the Delay Tool.** J. D. Klein, J. R. Beshansky, and H. P. Selker. Departments of Pediatrics and Medicine, New England Medical Center, Boston, Mass.

10:00 **Education and Stress Management in Asthma: A Randomized Controlled Trial.** J. M. Perrin, W. E. MacLean, S. L. Gortmaker, K. N. Asher. Children's Service, Massachusetts General Hospital, Department of Pediatrics, Harvard Medical School, and Department of Behavioral Sciences, Harvard School of Public Health, Boston, Mass, and Departments of Psychology and Pediatrics, Vanderbilt University, Nashville, Tenn.

10:15 **Health Status and Adjustment: Dissecting a National Sample.** R. E. K. Stein, D. J. Jessop, and A. Leon. Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY.

10:30 **Parent Attitudes and Practices of Children as Pedestrians.** F. P. Rivara, A. B. Bergman, and C. Drake. Harborview Injury Prevention and Research Center and Departments of Pediatrics, Epidemiology, and Biostatistics, University of Washington, Seattle.

10:45 **Coping Strategies to Stress in Children With Juvenile Rheumatoid Arthritis.** A. L. Olson, J. Pope, and R. B. Klein. Department of Maternal and Child Health, Dartmouth Medical School, Hanover.

11:00 **Findings From a Self-Administered Screening Form to Assess the Onset of Breast-feeding.** J. M. Seacat, M. R. Neifert, and S. M. DeMarzo. Lactation Program, Women's Hospital at AMI St Luke's, Denver, Colo.

11:15 **Does a Pediatrician's Attire Impact Differently on Parents and Children?** P. Narula, R. Marino, and W. Rosenfeld. Department of Pediatrics, Winthrop-University Hospital, Mineola, NY.

11:30 **Parenting Stress in Physician Families.** J. R. Sande, R. D. Olsen, and G. P. Olsen. Department of Pediatrics, Mayo Clinic, Rochester, Minn.

11:45 **Can Demographic, Clinical and Psychosocial Data Predict Which Mothers Will Be Reliable in Their Clinical Judgments?** P. McCarthy, B. Forsyth, H. Bauchner, S. Sznajderman, N. Czarkowski, M. Baron, H. Fink, and D. Cicchetti. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.

APA DEBATE

Wednesday, May 3, 1989
8:15 PM-9:45 PM
Maryland Suite

RESOLVED: THAT SHORTENED RESIDENT WORKING HOURS WILL CONTRIBUTE TOWARD MORE EFFECTIVE PATIENT CARE AND BETTER EDUCATION FOR TRAINING PEDIATRICIANS.

Moderator: Steven P. Shelov, MD, APA President
Professor, Department of Pediatrics
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York

Pro Resolution

Catherine De Angelis, MD, Professor and Deputy Chairman, Department of Pediatrics, Johns Hopkins Medical Institute, Baltimore, Md

Ralph Feigin, MD, J. S. Abercrombie Professor and Chairman, Department of Pediatrics, Baylor College of Medicine, Houston, Tex

Con Resolution

James A. Stockman III, MD, Professor and Chairman, Department of Pediatrics, Children's Memorial Hospital, Chicago, Ill

Abraham Bergman, MD, Professor, Department of Pediatrics, University of Washington, Seattle

JOINT TOPIC SESSIONS

WITH AMERICAN PEDIATRIC SOCIETY AND SOCIETY FOR PEDIATRIC RESEARCH

Thursday, May 4, 1989

2 PM-5:30 PM

ADOLESCENT MEDICINE

Washington Ballroom

Moderators: Michael I. Cohen, MD, Felix Heald, MD, and Lonnie Zeltzer, MD

2:00 *__The Relationship Between Serum Lipids and Estrogen in Adolescents Treated for Anorexia Nervosa.__ M. R. Arden, F. I. Chasalow, I. R. Shenker, and M. S. Jacobson. State University of New York at Stony Brook, and Department of Pediatrics, Schneider Children's Hospital of Long Island Jewish Medical Center, New Hyde Park, NY.

2:15 *__Contraceptive Noncompliance by Black Female Adolescents.__ R. H. DuRant, S. Jay, and C. Seymore. Department of Pediatrics, Medical College of Georgia Hospital, Augusta, Ga, and UAMS, Arkansas Children's Hospital, Little Rock, Ark.

2:30 *__Pubertal Timing and Adolescent Risk Taking: Are They Correlated?__ C. E. Irwin, Jr, S. G. Millstein, and R. Turner. Department of Pediatrics, University of California, San Francisco.

2:45 *__Stress, Psychosocial Factors and Primary Immune Response.__ B. K. Snyder, K. J. Roghmann, and L. H. Sigal (sponsored by Elizabeth McAnarney). Department of Pediatrics, University of Rochester (NY) Medical Center.

3:00 __An Analysis of Adolescent Suicide Attempts: The Expendable Child.__ J. Woznica and J. Shapiro. Division of Adolescent Medicine, Children's Hospital of Los Angeles (Calif).

3:15 *__Low Gynecologic Age (Low-GA) and Vaginal Bleeding During Pregnancy.__ C. Stevens-Simon, E. R. McAnarney, and K. J. Roghmann. Department of Pediatrics, University of Rochester (NY) Medical Center.

3:30 *__Minimal Weight for Menses in Anorexia Nervosa (AN).__ R. E. Kreipe, B. H. Churchill, J. Strauss (sponsored by Gilbert B. Forbes). Department of Pediatrics, University of Rochester (NY) Medical Center, and Department of Psychology, Williams College, Williamstown, Mass.

3:45 *__Is Teenage Pregnancy a Neonatal Risk Factor?__ R. Gale, D. S. Seidman, S. Dollberg, Y. Armon, and D. K. Stevenson. Bikur Cholim Hospital, Jerusalem, Israel, and Department of Pediatrics, Stanford (Calif) University School of Medicine.

4:00 *__Hormonal and Anthropometric Correlates to Adolescent Gynecomastia.__ F. M. Biro, A. W. Lucky, G. A. Huster, and J. A. Morrison. Department of Pediatrics, University of Cincinnati College of Medicine, Children's Hospital Medical Center, Cincinnati, Ohio.

4:15 __AIDS and Sexual Behavior Changes in Adolescents.__ D. Bunch, G. Zimet, T. Anglin, R. Lazebnik, P. Williams, and D. Krowchuk. Department of Pediatrics, Case Western Reserve University School of Medicine and Cleveland (Ohio) Metropolitan General Hospital.

4:30 *__Emotions, Acting Out and Abuse.__ R. Hibbard, G. Ingersoll, and D. Orr. Indiana University School of Medicine, Indianapolis, Ind.

4:45 __Children of School-age Mothers: Multiproblem Adolescents.__ S. M. Horwitz, L. V. Klerman, and J. F. Jekel. Department of Epidemiology and Public Health, Yale School of Medicine, New Haven, Conn.

5:00 *__Street Kids: Sex and Sexually Transmitted Diseases (STD): What They Know and Do.__ N. E. MacDonald, W. R. Bowie, and J. A. Doherty (sponsored by Robert G. Peterson). Expert Interdisciplinary Advisory Committee on STD in Children and Youth, Health and Welfare Canada, Ottawa, Canada.

5:15 *__Involuntary Smoking Alters Lipid Profiles in Adolescents.__ M. S. Jacobson, J. G. Feldman, R. A. Etsel, D. E. Lilienfield, F. Spierto, M. P. Nussbaum, and I. R. Shenker. State University of New York at Stony Brook and Brooklyn, Schneider Children's Hospital, Long Island Jewish Medical Center, New Hyde Park, NY, and Centers for Disease Control, Atlanta, Ga.

*Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, *Pediatric Research*, April 1989.

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

Virginia Suite

Moderators: James L. Mills, MD, Frederick P. Rivara, MD, and, John L. Sever, MD

2:00 *__Long-term Effects of Low Level Lead Exposure: 10-Year Follow-up.__ H. Needleman, A. Schell, and D. Bellinger. University of Pittsburgh (Pa), and Department of Neurology, Harvard Medical School, Boston, Mass.

2:15 *__Free-Running Test for Asthma Screening in School Children.__ A. C. Sukanich, K. D. Rogers, and P. Fireman. University of Pittsburgh School of Medicine, Children's Hospital, Pittsburgh (Pa).

2:30 *__A Survey of Dieting Behavior and Eating Attitudes in Children.__ M. J. Maloney, J. McGuire, S. R. Daniels, and B. Specker (sponsored by William K. Schubert). Departments of Psychiatry and Pediatrics, University of Cincinnati College of Medicine, Children's Hospital Medical Center, Cincinnati, Ohio.

2:45 *__Hypertension in Pregnancy: Whites Have Worse Outcome.__ L. Jain, D. Vidyasagar, and C. Ferre. University of Illinois Medical Center, Illinois Masonic Hospital, and Center for Perinatal Research, Chicago, Ill.

3:00 *__The Effect of Maternal Work During Pregnancy on Fetal Growth and Duration of Pregnancy.__ L. J. Launer, J. Villar, E. Kestler, and M. de Onis (sponsored by J. Mills). National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md, and the Centers for Disease Control, Atlanta, Ga.

3:15 *__Is Maternal Anemia a Risk Factor for Preterm Birth?__ M. A. Klebanoff, P. H. Shiono, H. W. Berendes, and G. G. Rhoads (sponsored by J. L. Mills). National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md.

3:30 *__Outcome of Infants Delivered to US Urban HBsAg-Positive Mothers.__ N. C. Christopher, P. L. Kral, R. P. Cleveland, N. V. Dawson, and M. L. Kumar. Case Western Reserve University School of Medicine, and Department of Pediatrics, Cleveland (Ohio) Metropolitan General Hospital (CMGH).

3:45 *__Prospective Longitudinal Follow-up of Pregnant Women Infected With Human Immunodeficiency Virus (HIV).__ A. Willoughby, H. Mendez, H. Minkoff, S. Holman, M. Berthaud, M. Gail, J. Goedert, and S. Landesman (sponsored by Leonard Glass). State University Health Sciences Center, Brooklyn, NY, National Institutes of Health, Bethesda, Md.

4:00 *__Risk of Cytomegalovirus (CMV) Infection in Employees of a Children's Hospital.__ K. Balcarek, R. Bagley, G. Cloud, and R. Pass. Department of Pediatrics, University of Alabama, Birmingham.

4:15 *__Epidemiology of CMV Transmission in Iowa Day Care.__ J. R. Murph and J. F. Bale, Jr. University of Iowa College of Medicine, Department of Pediatrics, University of Iowa Hospitals and Clinics, Iowa City.

4:30 *__Risk of *H Influenzae* Type B (HIB) Disease (DIS) in Children Attending Day Care in Dallas County, Texas (DAL) and Minnesota (MN).__ T. V. Murphy, M. T. Osterholm, and D. M. Granoff. University of Texas Southwest Medical Center, Dallas, Minnesota Department of Health, Minneapolis, and Washington University School of Medicine, St Louis, Mo.

4:45 *__The Resurgence of Acute Rheumatic Fever: Results of a Survey of Pediatric Cardiologists.__ R. E. W. Kavey and E. L. Kaplan (sponsored by W. Bergstrom). Department of Pediatrics, State University of New York Health Sciences Center, Syracuse, New York, and University of Minnesota Medical School, Minneapolis.

5:00 __Needlestick Injuries Among Pediatric House Officers in New York City.__ S. Melzer, S. H. Vermund, and S. P. Shelov. Department of Pediatrics, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY.

5:15 __Bunk Bed Injuries.__ S. M. Selbst and M. D. Baker. Emergency Department, Children's Hospital of Philadelphia (Pa), University of Pennsylvania.

*Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, *Pediatric Research*, April 1989.

BEHAVIORAL PEDIATRICS

Delaware Suite

Moderators: Ronald G. Barr, MD, Antoinette Eaton, MD, and John H. Kennell, MD

2:00 *__Rate of Cooling on Cardiopulmonary Bypass During Cardiac Surgery Associated With Changes in Developmental Outcome and Temperament.__ L. A. Rappaport, D. C. Bellinger, G. Wernovsky, P. Lang, P. R. Hickey, R. A. Jonas, and J. W. Newburger. Children's Hospital, Boston, Mass.

2:15 *__Voluntary Immunomodulation in Adolescents.__ K. Olness, H. R. Hall, and L. Minnes. Case Western Reserve University, Rainbow Babies and Children's Hospital, and University Hospitals of Cleveland (Ohio).

2:30 *__How Children Perceive the Medical Evaluation for Suspected Sexual Abuse.__ R. Lazebnik, J. Ebert, T. Anglin, P. Williams, G. Zimet, D. Bunch, and D. Krowchuk (sponsored by Elizabeth Danish).

Case Western Reserve University School of Medicine, and Department of Pediatrics, Cleveland (Ohio) Metropolitan General Hospital.

2:45 **The Impact of School-Based Education on Death Concept Formation in Early Elementary School-aged Children.** D. J. Schonfeld and M. Kappelman. Department of Pediatrics, Division of Behavioral and Developmental Pediatrics, University of Maryland, Baltimore.

3:00 **Impact of Type and Severity of Infant Disability on Differences in Family Adaptation.** J. Shonkoff, P. Hauser-Cram, M. Krauss, and C. Upshur. Division of Developmental and Behavioral Pediatrics, University of Massachusetts Medical School, Worcester.

3:15 **Psychosocial Problems During Child Health Supervision Visits.** L. Sharp, R. Pantell, and L. Olsen. Department of Pediatrics, University of California, San Francisco.

3:30 *__Labor Support: What's Good for Mother Is Good for Baby.__ J. Kennell, S. McGrath, M. Klaus, S. Robertson, and C. Hinkley. Case Western Reserve University, Cleveland, Ohio, Children's Hospital, Oakland, Ca, Cornell University, Ithaca, NY, and Baylor University, Houston, Tex.

3:45 *__Efficacy of Stimulant Medication Among Mentally Retarded (MR) Children With Attention-Deficit Hyperactivity Disorder (ADHD).__ B. L. Handen, A. M. Breaux, and Amy Gosling (sponsored by Richard H. Michaels). University of Pittsburgh, and Department of Pediatrics, Children's Hospital of Pittsburgh (Pa).

4:00 *__Prevalence of Dyslexia in Boys and Girls in an Epidemiologic Sample: Contrast Between Research Identified (RI) and School Identified (SI) Children.__ S. E. Shaywitz and B. A. Shaywitz. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.

4:15 *__Familial Basis for Severe Speech Disorders.__ B. Lewis and D. Aram (sponsored by M. Hack). Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio.

4:30 **Abnormalities of Growth in Homeless Children.** A. H. Fierman, L. M. Quinn, S. W. Shulman, C. Courtlandt, and B. P. Dreyer. Department of Pediatrics, New York University School of Medicine, Bellevue Hospital Center, New York, NY.

4:45 *__Psychiatric Disorders in Infants <1000 g BW Born in the 1980s: A Regional Perspective.__ P. Szatmari, S. Saigal, P. Rosenbaum, and D. Campbell. Departments of Pediatrics and Psychiatry, McMaster University, Chedoke-McMaster Hospitals, Hamilton, Canada.

5:00 *__Long-term Effect of Iron Deficiency Anemia in Infancy.__ B. Lozoff, F. Jimenez, A. Wolf, and N. Klein. Case Western Reserve University, Cleveland, Ohio, and National Children's Hospital, Costa Rica.

5:15 **The Effects of Early Communication Between a Provider and Mother in the Neonatal Period.** J. R. Serwint, M. Wilson, A. K. Duggan, D. E. Mellits, and C. DeAngelis. Department of Pediatrics, Johns Hopkins Hospital, Baltimore, Md.

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

Maryland Suite

Moderators: Barbara Korsch, MD, Paul McCarthy, MD, and Paula Stillman, MD

2:00 **A Prospective Evaluation of the Efficacy of Noninvasive In-Hospital and Outpatient Management of Febrile Infants.** M. D. Baker, L. M. Bell, and J. R. Avner. Divisions of General Pediatrics, Emergency Medicine, and Infectious Diseases, Children's Hospital of Philadelphia (Pa).

2:15 **Inpatient (I) Versus Combined Inpatient/Outpatient Therapy (CIO) of Serious Infections in Children.** K. A. Woodin, C. J. Davis, D. K. Bauserman, A. P. Higgins, J. A. McMillan, and K. R. Powell. Departments of Pediatrics and Preventive Medicine, University of Rochester (NY), and Pediatrics, State University of New York Health Science Center, Syracuse.

2:30 **Predictors of Pneumonia in Infants Less Than 12 Weeks of Age With Acute Respiratory Infection.** S. Berman, M. B. Shanks, D. Feiten, G. Horgan, and C. Rumack. Departments of Pediatrics and Radiology, University of Colorado School of Medicine and University Hospital, Denver, Colo.

2:45 *__Value of Routine Coagulation Testing Before Tonsillectomy.__ C. D. Burk, L. Miller, S. D. Handler, and A. R. Cohen. University of Pennsylvania School of Medicine, Philadelphia, and Departments of Pediatrics and Surgery, Children's Hospital of Philadelphia.

3:00 **Improving Outcomes in Asthmatic Patients: Results of a Randomized Trial.** R. Pantell, C. Lewis, and L. Sharp. Department of Pediatrics, University of California, San Francisco.

3:15 **Maternal Smoking and Childhood Asthma.** M. Weitzman, S. Gortmaker, D. K. Walker, and A. Sobel. Department of Pediatrics, Boston (Mass) City Hospital and Boston University School of Medicine, and Harvard School of Public Health, Boston.

3:30 *__Independent Practice Association (IPA) Insurance and Ambulatory Visits of Children Receiv-__

*Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, *Pediatric Research*, April 1989.

ing Hyposensitization. P. G. Szilagyi, K. J. Roghmann, and H. R. Foye (sponsored by Elizabeth R. McAnarney). University of Rochester (NY) Medical Center.

3:45 **Patterns of Crying in Colic: Implications for Etiology.** M. A. Geertsma, J. S. Hyams, B. Bernstein, and N. Etienne. Departments of Pediatrics, St Francis Hospital, Hartford Hospital, University of Connecticut Health Center, Hartford and Farmington, Conn.

4:00 **Can Every Woman Breast-feed?: The Incidence of Early Lactation Insufficiency.** S. M. DeMarzo, M. R. Neifert, and J. M. Seacat. Lactation Program, Women's Hospital at AMI St Luke's, Denver, Colo.

4:15 **Analgesic Use in the Emergency Department.** S. M. Selbst and M. Clark. Emergency Department, Children's Hospital of Philadelphia, and Medical College of Pennsylvania, Philadelphia.

4:30 **Parental Presence During Medical Procedures.** K. A. Merritt, J. R. Sargent, and L. M. Osborn. Department of Pediatrics, University of Utah School of Medicine, Salt Lake City.

4:45 *__Can a 'Western Medicine' Perinatal Outreach Education Program Be Effective in the 'Third World Countries' of Micronesia?__ R. B. Boychuk. University of Hawaii, Honolulu.

5:00 *__Short Stature and Income Among Men.__ E. Ekwo, N. Roizen, and C. Gosselink (sponsored by Arthur Kohrman). Department of Pediatrics, La Rabida Children's Hospital and Research Center, Chicago, Ill.

5:15 **'Night People': Pediatric Emergency Department Utilization During the Night.** L. M. Pachter and S. Ludwig. Division of General Pediatrics and Emergency Medicine Subdivision, The Children's Hospital of Philadelphia (Pa).

GENERAL PLENARY SESSION

Friday, May 5, 1989

8:15 AM-Noon

Virginia Suite

Moderator: Paul McCarthy, MD

8:15 **Carrying as Colic 'Therapy': A Randomized Controlled Trial.** R. G. Barr, U. A. Hunziker, S. J. McMullan, H. Spiess, D. G. Leduc, J. Yaremko, R. Barfield, T. E. Francoeur, and P. Rossy. Department of Pediatrics, Montreal (Canada) Children's Hospital.

8:30 **Bicycle Helmet Use by Children: Evaluation of a Community-Wide Helmet Campaign.** C. DiGuiseppi, F. Rivara, and T. Koepsell. Harborview Injury Prevention and Research Center and Departments of Pediatrics, Epidemiology, and Health Services, University of Washington, Seattle, and Children's Hospital National Medical Center and Department of Child Health and Development, George Washington University, Washington, DC.

8:45 **Is Childhood Obesity Protective or an Added Risk Factor for Adult Hypertension? A Study Over 50 Years.** J. H. Straus and E. Charney. Department of Pediatrics, Fallon Clinic, and the University of Massachusetts Medical School, Worcester.

9:00 **Social and Environmental Risks for Childhood Asthma.** M. Weitzman, S. Gortmaker, D. K. Walker, and A. Sobol. Department of Pediatrics, Boston (Mass) City Hospital and Boston University School of Medicine, and Harvard School of Public Health, Boston.

9:15 **Parents' Vs Physicians' Utilities (Values) for Clinical Outcomes in Potentially Bacteremic Children.** M. S. Kramer, A. M. MacLellan, and D. G. Leduc. Departments of Pediatrics, and Epidemiology and Biostatistics, McGill University Faculty of Medicine, Montreal, Canada.

9:30 **PRESIDENT'S ADDRESS**

10:00 **INTERMISSION**

10:15 **Utilization of Health Services by Children Who Were Identified During the Postpartum Period as Being at High Risk of Child Abuse or Neglect.** J. M. Leventhal, A. T. Berg, C. Brady, and R. M. Garber. Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.

10:30 **Predictors of Long-term Success Among School-age Mothers.** S. M. Horwitz, J. F. Jekel, L. V. Klerman, and H. S. Kuo. Departments of Epidemiology and Public Health, Yale School of Medicine, New Haven, Conn.

10:45 **Improving Patient Outcomes Through Improved Communication: Randomized Controlled Study of an Educational Intervention.** C. Lewis, R. Pantell, and L. Sharp. Department of Pediatrics, University of California, San Francisco.

11:00 **Who Subsidizes Ambulatory Pediatric Research?** R. E. K. Stein and S. S. Kessel. Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY, and Bureau of Maternal and Child Health and Resources Development, Rockville, Md.

11:15 **Injuries in Child Care Centers.** R. Pantell, C. Lewis, and C. Gilliss. Department of Pediatrics, University of California, San Francisco.

11:30 **Vision Screening at Preschool Health Supervision Visits: A Collaborative Study.** R. C. Wasserman and C. A. Croft. Pediatric Research in Office Settings (PROS) Network, American Academy of Pediatrics, Elk Grove Village, Ill.

11:45 **Career Patterns of Men and Women Members of the Ambulatory Pediatric Association.** R. E. K. Stein. Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY.

*Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, *Pediatric Research*, April 1989.

SCHEDULE OF EVENTS—1989 ANNUAL MEETING
THE AMERICAN PEDIATRIC SOCIETY AND
THE SOCIETY FOR PEDIATRIC RESEARCH

Monday May 1	Tuesday May 2	Wednesday May 3	Thursday May 4
	8 AM-9 AM APS Presidential Address St Geme Award and 100-Year Pediatric History (Sheraton Ballroom) 9 AM-11:30 AM Poster Symposia 4-8 9 AM-2 PM Poster Session II Commercial Exhibits (Exhibit Hall) 9:15 AM-11:30 AM APS Presidential Symposia (Sheraton Ballroom)	8 AM-9:15 AM SPR Presidential Address Young Investigator Award Other Awards (Sheraton Ballroom) 9 AM-2 PM Poster Session III Commercial Exhibits (Exhibit Hall) 9:30 AM-Noon SPR Presidential Symposia (Sheraton Ballroom) Poster Symposia 9-12	8 AM-11:30 AM Subspecialty Platform Sessions III
	11:30 AM-1 PM APS Business Meeting (Sheraton Ballroom)		11:30 AM-1 PM SPR Business Meeting (Sheraton Ballroom)
1:30 PM-5:30 PM Joint Sessions With American Federation for Clinical Research, American Society for Clinical Investigation, and American Academy of Pediatrics Endocrinology Genetics Hematology Immunology Infectious Diseases Metabolism Renal and Electrolytes	1:30 PM-2 PM APS Howland Award (Sheraton Ballroom) 2:15 PM-5:45 PM Subspecialty Platform Sessions I	1:30 PM-5 PM Subspecialty Platform Sessions II	2 PM-5:30 PM Subspecialty Platform Sessions IV
5:30 PM-8 PM Poster Session I Commercial Exhibits (Exhibit Hall) 7 PM-9:30 PM Poster Symposia 1-3			

THE AMERICAN PEDIATRIC SOCIETY AND THE SOCIETY FOR PEDIATRIC RESEARCH

SUBSPECIALTY PLATFORM SCHEDULE—1989

SESSIONS I

Tuesday, May 2
2:15 PM-5:45 PM

Cardiology I
(Marshall)
Developmental Biology I
(Atrium II)
Endocrinology I
(Washington Ballroom)
Gastroenterology/Nutrition I
(Maryland Suite)
Genetics I
(Atrium I)
Hematology/Oncology I
(North Cotillion)
Immunology I
(South Cotillion)
Neonatology-General I
(Sheraton Ballroom)
Nephrology I
(Delaware Suite)
Pulmonology I
(Virginia Suite)

SESSIONS II

Wednesday, May 3
1:30 PM-5 PM

Cardiology II
(Atrium I)
Developmental Biology II
(Atrium II)
Dysmorphology and Teratology
(Marshall)
Immunology II
(Virginia Suite)
Infectious Diseases I
(Washington Ballroom)
Metabolism & Diabetes I
(North Cotillion)
Neonatology-General II
(Sheraton Ballroom)
Nephrology II
(Delaware Suite)
Neurology
(South Cotillion)
Pulmonology II
(Maryland Suite)

SESSIONS III

Thursday, May 4
8 AM-11:30 AM

Critical Care
(Delaware Suite)
Developmental Pharmacology I
(Atrium I)
Endocrinology II
(North Cotillion)
Gastroenterology/Nutrition II
(Maryland Suite)
Genetics II
(Atrium II)
Hematology/Oncology II
(South Cotillion)
Neonatal Epidemiology and Follow-up
(Washington Ballroom)
Neonatal Infectious Diseases
(Virginia Suite)
Neonatal Pulmonology
(Sheraton Ballroom)

SESSIONS IV

Thursday, May 4
2:00 PM-5:30 PM

Adolescent Medicine
(Washington Ballroom)
Behavioral Pediatrics
(Delaware Suite)
Developmental Pharmacology II
(Marshall)
Epidemiology and Preventive Pediatrics
(Virginia Suite)
General Pediatrics and Pediatric Education
(Maryland Suite)
Infectious Diseases II
(North Cotillion)
Metabolism and Diabetes II
(Atrium II)
Neonatal Cardiology
(Atrium I)
Neonatal Immunology/Hematology
(South Cotillion)
Neonatal Nutrition and Metabolism
(Sheraton Ballroom)

Annual Meeting of the Ambulatory Pediatric Association

ADOLESCENT MEDICINE AND PEDIATRIC EDUCATION

Anabolic Steroids and High School Students

L. G. McLain

Department of Pediatrics, Loyola University Stritch School of Medicine, Maywood, Ill

Few topics have recently received as much publicity in the lay sporting press as anabolic steroids. In spite of this, there are few studies in the scientific literature with meaningful data about actual useage in adolescents. To assess this situation a 29 question survey about anabolic steroids was given to 2,113 students, athletes and non-athletes, in a four year high school. The survey was administered so that confidentiality was guaranteed. Analysis of some of the data revealed: 1) An equal distribution of males—1013 and females—1062 (38 no response) 2) An equal distribution among the four years; freshmen—534, sophomores—496, juniors—518, seniors—542 (23—no response). 3) 332 students (15.7%) reported they knew someone who use steroids 4) 732 students (34.6%) stated that it would be easy to obtain steroids if they wanted them. 5) Eighty-six (68 males, 18 females) admitted taking steroids for an overall incidence of 4.1%. 6) Of the 86 who took steroids, there were 19 freshmen, 21 sophomores, 23 juniors, 23 seniors. 7) Of the 86 who took steroids, 71 participated in sports and 15 did not 8) Of the 86 who took steroids, 21 obtained them from a coach, 30 from a physician, 39 from friends, 23 other (more than one answer was possible) 9) 752 students participated in sports. In this group, 71 took steroids for an incidence of 9.4%. This study suggests significant use of anabolic steroids in high school students.

Pediatricians' Views of Appropriate Access to Care for Adolescents

G. V. Fleming, K. G. O'Connor, J. M. Sanders

Department of Research, American Academy of Pediatrics, Elk Grove Village, Ill

Pediatricians' views of appropriate access to care for adolescents are important because adolescents generally show low levels of utilization of medical services and often have serious health problems (e.g. teenage pregnancy, substance abuse problems, other behavioral problems), and pediatricians are an important source of care for this group. The American Academy of Pediatrics (AAP) (representing about 80% of Board certified pediatricians) carried out two member surveys on issues in adolescent access to care, including: (1) school-based clinics, (2) parental permission and (3) TV advertising of contraceptives. Response rates were over 70%, yielding total Ns of over 700.

Pediatricians were generally favorable to the use of school-based clinics, e.g., only 31% thought they compromised continuity of care, although an equal percent were "neutral." 58% thought they should dispense contraceptives. Pediatricians generally agreed adolescents 17-18 years "should be able to contract for their own health care without parental permission" (74%), although only 26% agreed to the same statement for adolescents 13-16 years. The same pattern was evident in related statements. Pediatricians were also generally favorable to advertising contraceptives on TV, e.g. 67% agreed that TV contraceptive ads help reduce teen pregnancies and 66% disagree that TV contraceptive ads promote teen sexual promiscuity. Female pediatricians were consistently slightly more likely to endorse school-based clinics and be favorable to direct adolescent access to services and information than were male pediatricians, and younger pediatricians were more likely to favor these points of view than older pediatricians. If these attitudes are stable, we may expect pediatricians in the future to be increasingly favorable to school-based clinics and to adolescent direct access to care and information.

Risk Factors for C. trachomatis Cervical Infection in Adolescent Females

M. K. Oh, R. A. Feinstein, E. J. Soileau, G. Cloud, R. F. Pass

Department of Pediatrics, Division of Adolescent Medicine, Division of Infectious Disease, University of Alabama, Birmingham

To determine risk factors for C. trachomatis (CT) infection among adolescent females, sexually active girls attending a family planning clinic for teenagers (12-18 years, mean 16 ± SD 1.3) were screened for sexually transmitted diseases (STDs). During the study period of 28 months, 333 patients made 445 scheduled visits requiring pelvic examination for their routine care. Endocervical specimens obtained during each encounter were cultured for CT. CT was isolated from 85 (25.5%) of 333 patients or 94 (21.1%) of 445 encounters. To determine risk factors for CT infection, demographic, behavioral and clinical variables among CT positive and CT negative groups were analyzed and compared. Students t-test, chi-square analysis, and logistic regression analysis were used as appropriate to test for association between CT infection and factors potentially related to CT infection, and to further define the relationships with CT infection while simultaneously accounting for the other confounding factors.

CT infection was associated with cervicitis ($p<.0001$), GC ($p<.0001$) and Trichomonas ($p=.003$) infections, more than 5-mon use of oral contraceptives (OC) ($p=.02$), and less than 4-years of sexual activity ($p=.02$). Age of patients, sex partner's age, race and a history of pregnancy were not associated with CT infection. Logistic procedure showed that more than 5-months use of OC ($p=.01$) and less than 4-years of sexual activity ($p=.03$) remained independently significant variables after accounting for other confounding variables. Our study suggests CT infection rate and/or isolation rate of CT from the genital tract is significantly greater during the first 3 years of sexual activity ($RR=3.8$). CT infection in this population is also associated with OC use of 6-mon or longer ($RR=1.6$), as well as infection by other STD agents. On the contrary, duration of sexual activity and OC use were not significantly associated with GC or Trichomonas infections (7% and 13% prevalence respectively). A screening for CT must be a part of medical care for sexually active teenagers.

Adolescents Who Smoke 'Crack': Patterns and Consequences of Use

R. H. Schwartz, N. G. Hoffman, M. Luxemburg

Department of Pediatrics, Fairfax (Va) Hospital, STRAIGHT Inc, Springfield, Va, and CATOR, St Paul, Minn

Cocaine free-alkaloid commonly known as "crack" was smoked by an estimated 100,000 high school students in 1987. We administered a questionnaire concerning the use of "crack" to 464 chemically-dependent, middle-class, adolescents in a chain of outpatient drug-abuse treatment facilities in order to obtain information on pattern of use, addictive potential of the drug, and medical or psychosocial consequences of such use. One third of the respondents denied any serious childhood problems antedating drug abuse; however, 38% believed that one or both parents were alcoholics and 31% recalled that they themselves had suffered from chronic childhood depression. Twenty-one percent admitted to legal problems before initiation of drug abuse. Of the 336 (75% of the 464 respondents) who used cocaine at least once, 130 (38%), had smoked "crack." Approximately 50% of the 87 individuals who smoked "crack" from 1-9 times ("experimenters")- Vs. 90% of the 23 who used it more than 50 times* (heavy users), recalled preoccupation by thoughts of cocaine, inability to save "crack" for later, and the development of tolerance to the euphoric action of the drug. Twenty percent of the experimenters Vs. 60% of the heavy users* had spent an average of more than $100/wk. on cocaine**. "Crack" is highly addicting: 12% of the experimenters and 60% of the heavy users** progressed from first use to weekly use within 90 days. Use of "crack" is a risk factor for AIDS: 7% of the experimenters Vs. 23% of the heavy users** began to inject drugs intravenously. Seventy-two percent of the heavy users noted a weight loss of 15# or more. Nine percent of adolescents in this group experienced a brain seizure during "crack" use. After cocaine use began, 20% of the experimenters Vs. 40% of the heavy users had shoplifted at least $500 worth of goods and/or had stolen an automobile and had not returned it.***

Chi Square Test * $P<.005$, ** $P<.0001$, *** $P<.05$

Rehabilitation of Chemically Dependent Adolescents: A Follow-up Survey

D. E. Smith, R. H. Schwartz, M. E. Gutgesell

Department of Pediatrics, University of Virginia Health Sciences Center, Charlottesville

To determine if rehabilitation of addicted youth allows normal development, we surveyed and compared two groups of chemically-dependent teenagers, program completers (PC) and noncompleters (NC), admitted to a day treatment program.

Of 316 adolescents admitted consecutively over 20 months to Straight, Inc., 187 (59%) responded to a questionnaire 1.5 to 4 years after leaving the program. There were 133 PC (71%) and 54 NC (29%). At entry, mean age was 16.6 ± 2.5 years. Most were white (99%), male (70%) and living at home (83%). Drugs of abuse were alcohol (99%) and marijuana (97%). At followup, mean age was 20.5 ± 2.4 years; 61% were male. Before treatment, 29% reported school dropout (mean grade, 9.5 ± 1.4). At followup, 159 (85%) reported high-school completion or equivalent. Full-time employment was reported by 71% (132/187), with 74% (118/160) earning above minimum wage. Only 10 of 184 were unemployed; 48% (88/164) had job stability for over 10 months. Improved ability to repay debts was reported by 88 of 186 (47%).

PC (120/133) reported better communication with parents than NC (41/54) ($\chi^2 = 6.545$; $p<0.05$). More NC reported fights with boy- or girl friends: 17/51 vs 18/131 ($p<0.01$). Sexual experience (number of partners, incidence of STDs, pregnancy) was similar in the groups. PC found treatment more useful than NC: 71% vs 45% ($p<0.01$). The groups reported similar numbers of drug-using friends. Social drinking and peer-group pressure were the most common causes for relapse, occurring in 81 (43%). Continuing drug use was reported by 19% (25/130) PC and 30% (16/53) NC. Over 60% (72/119) PC claimed abstinence for the past year compared with 9% (5/39) NC ($p<0.001$). Tobacco use was prevalent in both groups; alcohol was used by 87% NC but only 44% PC.

Adolescents who participated in a day treatment drug program had improved school success and employment. PC had better social relationships and were less likely to return to drug use.

Percentage Body Fat Determinations in 4,360 Adolescent Athletes

B. A. Spear, R. A. Feinstein

Department of Pediatrics, University of Alabama, Birmingham

Percent body fat (%BF) recommendations exist for the adolescent population, but limited research has been conducted in determining body composition in the scholastic adolescent athlete. Unfortunately, most recommendations for adolescent athletes are based on age and have been extrapolated from older adolescents (17-22 years) or from elite athletes such as college freshmen or junior olympic athletes. The purpose of this study was to determine the relationship between maturation (SMR) and %BF of junior and senior high school football players. %BF determinations were made on 4,360 scholastic football players aged 11 to 19 years participating in an annual preparticipation physical examination program from 1985-88. Maturation (SMR) was assessed by a physician using Tanner staging. Biceps, triceps, subscapular and suprailiac skinfold measurements were made using a Lange caliper. %BF was computed by utilizing the equation of Durnin and Womersley. In this present study mean %BF was 20.79%. A statistically significant relationship existed between %BF and SMR ($p<0.001$). Athletes with SMR 1 ($24.1\% \pm 7.8$) and SMR 2 ($22.6\% \pm 7.3$) exhibited a greater %BF than athletes with a SMR of 3 ($20.83\% \pm 6.2$), 4 ($20.37\% \pm 5.6$) or 5 ($20.82\% \pm 5.1$). No significant statistical differences existed between SMR's 1 and 2, SMR's 3 and 4 or SMR's 3 and 5. A significant statistical difference existed between SMR's 4 and 5 ($p<0.05$). No significant statistical relationship existed between any chronological ages and %BF. Published standards are used by coaches to counsel athletes about appropriate body composition. Our study challenges the present recommendations concerning optimal %BF for adolescent athletes and demonstrates the need to use level of SMR in establishing future recommendations.

Safer Sex and Adolescent Condom Use

A. Joffe, S. M. Radius, M. Gall

Department of Pediatrics, Johns Hopkins Medical Institutions, Baltimore, Md

As condom use decreases risk of contracting AIDS, we attempted to identify factors influencing adolescents' condom use. Data derived from questionnaires completed by 487 (294 males) of incoming college freshmen (66% of class). Selection of variables was guided by Health Belief Model elements of perceived susceptibility to & severity of AIDS, and perceived benefits & barriers of condom use. Also examined were peers' use & personal attitudes re: sexuality & safer sex practices. Among all respondents, males were more likely than females to state that they had "heard enough" about AIDS ($p<.0037$) but worried more about contracting this disease ($p<.003$). In support of safer sex practices, males more than females indicated greater peer use of condoms ($p<.0005$) and willingness to obtain condoms from vending machines ($p<.00001$). In contrast, females exceeded males in feeling less anxious about sex with condom use ($p<.02$) and perceiving discussions about condom use as reassuring to partners ($p<.0038$). Males more than females reported condom use as "turn-offs" for

themselves ($p<.0001$) and to their partners ($p<.00001$).

86% of males and of females reported they were likely/very likely to use at next intercourse. A full regression model, comprised of all significantly correlated independent variables explained 48% ($p<.00001$) of sexually active males' condom use at next intercourse. Most influential ($p<.01$) were frequency of prior condom use and feeling less anxious about sex with condoms. 52% ($p<.0002$) of sexually active females' future use was explained by these same independent variables.

While comparable proportions of males and females report their likely future use of condoms, females maintain more favorable attitudes toward their use. Males continue to express relatively more negative feelings regarding condom use, suggesting the need for sex-specific educational interventions to encourage this safer sex practice among adolescents.

Teaching About Sexuality and AIDS: A Comparison of Health Professionals and Peer Educators

D. M. Siegel, J. Neuderfer, W. H. Zimmerli, D. Gilson

Department of Pediatrics, Rochester General Hospital, University of Rochester (NY)

A physician/nurse practitioner pair designed and conducted a 6 class learning unit covering aspects of sexuality, including AIDS, for secondary school students taking health in a predominantly white middle class suburban high school. The program consisted of a 49-item pretest (33 cognitive and 16 attitudinal/behavioral/demographic questions) followed by 4 classes presented by the investigators (2 lectures, 2 videotape sessions) covering methods of family planning, sexually transmitted diseases, and AIDS. The pretest was then readministered 2 weeks following the last class and again at the conclusion of the school year. 202 students (Group 1) were taught by the health professional pair in the Fall of 1987 and 111 students (Group 2) were taught by a volunteer high school student pair recruited from the Fall classes and trained by the investigators. The 2 groups of students were not significantly different with regard to age (mean age:17.2 years), gender (56%male), or socioeconomic status. Students taught by both types of instructor teams showed a significant increase in knowledge between the pretest and post test ($p<0.001$) and the increase persisted on the second post test. The pretest scores and the post test improvements were not predicted by standardized aptitude test scores obtained on each student during the school year ($R^2=5.2\%$). Each group reported similar rates of being sexually active (68% in group 1, 63% in group 2), while on the pretest, 31% of group 1 and 39% of group 2 underestimated the risk of pregnancy associated with unprotected sexual intercourse. Peer educators and health professionals were equally as successful in increasing knowledge of high school students concerning sexuality and AIDS, though school teachers rated the class discussions in the peer-taught sessions as more lively and involving. A comparable control group from 3 suburban high schools had significantly lower test scores than the post test scores of the 2 experimental groups.

Does Systematic Feedback Improve Clinical Teaching?

T. R. Schum, K. J. Yindra, R. G. Koss, D. B. Nelson

Department of Pediatrics, Medical College of Wisconsin, Milwaukee

In order to determine whether systematic feedback to faculty would improve their ratings for clinical teaching, we prospectively studied resident and student evaluations of faculty.

From April 1987 through October 1988 pediatric faculty in all clinical settings were rated on overall teaching effectiveness (OTE) and nine other traits using a 7 point Likert scale (7 = Outstanding). In November 1987, 44 faculty were randomly assigned to receive either feedback on their teaching every 2 months for the next 12 months or to receive no systematic feedback. Feedback included recent and cumulative summaries of their ratings, similar department mean ratings, and a ranking of OTE by quartile and comments. Mean trait ratings for each faculty member were determined. These were then averaged for feedback and control groups and compared using t-tests.

44 faculty received 1231 evaluations. Results are means ± SEM.

	Feedback (N = 21)		Control (N = 23)	
	BF	AF	BF	AF
OTE	5.65 ± .11	5.76 ± .12	5.68 ± .12	5.61 ± .11
Knowledge	6.00 ± .10*	6.22 ± .08	6.08 ± .08	6.10 ± .08
Demonstrates skills	5.75 ± .10*	6.03 ± .08	5.93 ± .10	5.87 ± .08
Gives feedback	5.10 ± .12*	5.44 ± .11	5.34 ± .13	5.42 ± .12

*$p<.05$, AF VS BF, BF = Before Feedback (Apr-Oct 87), AF = After Feedback (Nov 87-Oct 88)

The feedback group improved their ratings by an average of .14 ± .04 across all 10 categories whereas the control group had no change .00 ± .02, $p<.05$. For faculty initially below the department OTE mean, the feedback group increased their ratings by .28 ± .05 whereas the control group increased by .08 ± .03, $p<.05$.

We conclude that providing systematic feedback to faculty 1) did not lead to a significant increase in OTE ratings but 2) led to significantly improved ratings in knowledge, demonstrating skills, giving feedback and the average change across all 10 traits. The greatest improvement occurred in those faculty who were initially below the department OTE mean and then were given feedback.

Measured Outcome of a New Curriculum Varies Among Residents, Simulated Mothers, and Blind Coders

D. Kittredge, R. Olson, P. Buck, A. Cucchiara

Departments of Pediatrics, Psychiatry and Behavioral Sciences, and Bio-Statistics and Epidemiology, University of Oklahoma Health Sciences Center, Oklahoma City

A prospective study was done to measure changes in counseling skills in 54 pediatric residents exposed to a new curriculum for one year (19 PL-1's, 20 PL-2's, 15 PL-3's). The curriculum included teaching by trained mothers at 6 simulated well child visits, a manual for residents plus new counseling guidelines and prompts.

Counseling skills of each resident were measured at the first 2 (PRE) and last 2 simulated visits (POST), using an 18 item, 1-5 point (5 = high) behavior rating scale with 2 major subsets: basic communication skills (e.g., establishing rapport) and health education skills (e.g., emphasizing key points). The mother and resident rated the resident before feedback; a blind coder rated a videotape of the session. Interrater agreement for blind coders was 90.2%.

Blind coders rated residents at PRE lower in health education than basic communication skills (mean score 1.8 vs 3.4). Mothers and residents gave higher overall ratings, but also rated education skills lower. Ratings did not vary by training level.

The mean ratings on each resident at PRE and POST were compared (repeated measures ANOVA). Based on ratings by the residents and mothers, gains occurred overall and on subset scores ($p<.001$). Residents' ratings were higher on 16/18 items and mothers' on 17/18. PL-1's and 2's perceived greatest gains; mothers found no difference by training level. In contrast, blind coders found no overall, subset, or training level difference between PRE and POST. Item analysis showed loss in assessment skills; and gain in establishing rapport, using handouts, and closing the visit ($p<.01$).

Teaching mothers and residents perceived dramatic improvements following this intensive curriculum, but no overall gains

were observed when behaviors were measured more objectively. Programs using trained patients for teaching must be cautious about interpreting results based on ratings by participants.

How Do General Pediatric Clinics Function From the Perspective of the Practice Manager? Results of a Survey of Academic Departments

J. E. Berkelhamer

Department of Pediatrics, University of Chicago, Pritzker School of Medicine, Wyler Children's Hospital, Chicago, Ill

Academic pediatric departments located in the United States were surveyed to gather information regarding a number of issues relevant to the operation of their hospital-based general pediatric clinics (GPCs). These issues include educational efforts related to practice management, personnel allocation, financial performance, organizational formats, administrative arrangements, and access to primary care services for children of poor families. Three pre-survey hypotheses motivated this study. First, pediatric residents are only sporadically taught practice management skills. Second, GPCs would benefit from greater involvement in practice management by academic faculty. And third, GPCs are important sources for primary care services for many children.

94 of 131 surveys were returned (72% response rate). GPCs averaged 15,486 visits per year; and the number of visits overall has increased by 11.9% over the past 5 years. 47.5% of visits are acute visit related, 36.1% are for health maintenance, and 16.4% are for problems associated with chronic diseases. Residents have the primary responsibility for 55.6% of these visits. Educational efforts related to practice management vary considerably within GPCs; less than half report any. Educational activities occur around issues related to scheduling of patients, quality assurance, supervision of support staff, and the development of policies and procedures in the GPC. Little attention is given to issues related to accounts payable, budgeting, external audit review, staff recruitment, supplies, or union contracting. The overall staff ratios per faculty physician are similar to nonteaching practices but differ in composition due to training activities inherent to GPCs. GPCs average a loss of $250,000 per clinic. Organizational formats vary considerably; the majority of physician directors have no line-management authority for nursing and clerical staff.

Survey results confirm that GPCs serve a large number of poor children with 41.3% funded by Medicaid and 16.0% unable to pay out-of-pocket expenses. GPCs are generally not utilized to teach practice management, tend to lose money, and have little faculty involvement in their management.

Pregnancy During Pediatric Residency: Attitudes and Complications

J. Klevan, J. Weiss, S. Dabrow

Department of Pediatrics, Thomas Jefferson University, Philadelphia, Pa

Questionnaires designed to collect information about pregnancy during residency were mailed to 116 female physicians who completed their pediatric training in the Philadelphia area within the last five years. Ninety three (80%) of the physicians returned the questionnaire, which contained items focused on 1) maternal complications, 2) health of the baby, 3) attitudes towards the pregnancy experience.

Thirty five of the 93 respondents (38%) were pregnant during their residency. A majority (22/39) of the pregnancies occurred in the third year of training.

Seventeen complications occurred in 14 of the 39 pregnancies (36%), the most common complications being preterm labor (4 cases), preeclampsia (4 cases), and hyperemesis (5 cases). Other complications reported once each were Shigella gastroenteritis, pyelonephritis, gestational diabetes, and partial placental abruption. Of the 17 complications, 6 (35%) were serious enough to require hospitalization. Complications resulted in time lost from work in 40% (15/39) of the pregnancies. The mean amount of time missed from work was 4 weeks, but the range was from several days to 18 weeks.

Babies born to pediatric residents were generally in good health, however 10 out of 39 pregnancies (26%) resulted in miscarriage or stillbirth. Mean birth weight was 7.2 lbs and mean gestational age was 39 weeks. Almost all babies were breast fed (23/25) for a mean duration of 27 weeks.

When asked to describe the experience of being pregnant during residency, only 24% felt that it was "pleasant", while 52% said the experience was "tolerable" and 24% found it "miserable"! 37% (13/35) stated that they would not get pregnant during residency if they had it to do over again. Chi square analysis did not show a relationship between attitude towards pregnancy and either the training level or the incidence of maternal complications. However, those residents whose pregnancies did not result in a live birth were significantly less likely to state that they would "do it over again" (Chi square = 4.08, $p<.05$).

Results from this questionnaire study indicate that pregnancy during pediatric residency is a common event, but often not a pleasant one for the pregnant resident. Complications of pregnancy during residency are not rare and frequently result in hospitalization and loss of time from work. This has several implications for residency program directors including impact on schedules, morale, and the quality of education obtained by residents who are pregnant during their training.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Academic Achievement and Its Correlates in a Community Sample of Chronically Ill Children

M. C. Starr, F. C. Jarman

Department of Pediatrics, University of Massachusetts Medical School, Worcester

Little published data is available describing the academic functioning of representative samples of chronically ill children in the community. What are the true risks of school under-performance for these students, and what factors correlate with different academic outcomes?

We prospectively surveyed parents of *all* 1601 fourth grade public school students in Worcester, using a standardized health screening questionnaire. Three hundred six (26%) of 1167 children who returned questionnaires had broadly defined chronic medical problems. They were paired with healthy classroom controls matched for age, sex, race, and SES. Between and within group comparisons were made on measures of academic aptitude, achievement, placement in special education, school attendance, and other variables of interest.

No significant differences were found between groups on Otis Lennon Ability Test scores. Chronically ill children performed barely more poorly on Metropolitan Achievement Tests ($X^2 = 5.8$, $df = 2$, $p = 0.05$), were more likely to be enrolled in special education ($X^2 = 9.1$, $df = 1$, $p<0.003$, $RR = 1.7$), and were absent significantly more days over the preceding 12 months (10 vs 8 days; $F = 7.6$, $df = 1$, $p<0.006$). Absenteeism was significantly and negatively correlated with achievement for the chronically ill group ($r = -0.25$, $p<0.001$), but not for controls ($r = -0.05$, $p>0.05$). Multiple regression analysis revealed SES and absenteeism, but no other school or family variables, to explain independently significant proportions of the variance in achievement.

We conclude that chronically ill children underachieve relative to healthy controls despite commensurate abilities. Absenteeism for this group may be correlated with poor achievement because it serves as a measure of the ill child's real or perceived vulnerability, rather than the effects attributable to time lost from school.

The Effect of Mother's Health on the Care of a Chronically Ill Child

J. L. Lauby, L. J. Bauman, R. E. K. Stein

Department of Pediatrics, Preventive Intervention Research Center for Child Health, Albert Einstein College of Medicine, Bronx, NY

Health care providers are increasingly aware of the mental and emotional problems of children with chronic illnesses. However, the physical and mental strain on the child's caretaker, usually the mother, is often overlooked. When the mother has a chronic illness herself, the challenge of caring for an ill child becomes even greater. We hypothesized that when the mother of a chronically ill child is ill herself 1) she would have more difficulty caring for her child, 2) the impact of the child's illness on the family (measured by the Impact on Family Scale) would be greater, and 3) the mother's mental health (measured by the Psychiatric Symptom Index) would be negatively affected.

Data analyzed were from interviews with 70 mothers of chronically ill children under 12 years of age from an inner-city minority population. Twenty-six (37%) of the mothers had a chronic illness themselves and 16 (23%) rated their own health as only fair or poor. Mothers with a chronic illness were more often unable to afford medical care for their children ($p<.05$) and had more difficulty arranging child care ($p<.05$) than well mothers. Multiple regression analysis revealed that both mother's and child's health ratings were related to the impact of the child's illness on the family. Analysis done separately for ill mothers showed that mother's mental health was strongly related to the impact of the child's illness on the family ($B=2.16$, $p<.01$). This relationship was much weaker in the group of well mothers ($B=0.65$, $p<.07$).

These findings suggest that when both a mother and her child have a chronic illness, there are reciprocal effects that increase the risks for each. The mother's illness makes it more difficult for the child to get adequate care and the child's illness causes disruption in the family and affects the ill mother's mental health.

'Unrecognized' Chronically Ill Children in School: A Group At Risk for Psychosocial Difficulties

F. C. Jarman, M. C. Starr

Department of Pediatrics, University of Massachusetts Medical School, Worcester

A school's ability to provide an appropriate environment for students with special health care needs is dependent on its knowledge of the child's medical condition, and how this may affect learning and behavior. We tested the hypothesis that a substantial number of chronically ill children are unidentified as such by their schools. Parents of *all* 1601 4th grade children from the 41 public schools in Worcester were sent a standardized questionnaire designed to distinguish children with chronic illnesses from their healthy peers. Of the 1167 (73%) children whose parents returned questionnaires, 306 (26%) fulfilled diagnostic criteria for chronic illness, and were paired with healthy classroom controls matched for age, sex, race, and SES. Both groups were then compared on a number of family variables and standardized child measures, including multivariate indices of behavior.

Only 141 of 306 (46%) chronically ill children were identified by their schools; 35 (11%) by their teachers, and 125 (41%) by School Health Record review. "Unrecognized" chronically ill children were at the same increased risk for behavior disorder as the chronically ill known to their schools, even after controlling for confounding variables. On the parent version of the Child Behavior Checklist (CBCL), chronically ill children had more dysfunctional scores than control children on the Social Competence subscale ($F=12.9$ $df=1$ $p<0.001$), Internalizing subscale ($F=4.8$ $df=1$ $p<0.04$), and Total Behavior Problem index ($F=4.3$ $df=1$ $p<0.05$). Significant differences appeared across diagnostic categories. No differences were noted on the Teacher CBCL, perhaps reflecting their lessened awareness of "internalizing" disorders.

We conclude that schools may be unaware of the health status of a substantial proportion of children with chronic medical conditions who may be at risk for psychosocial difficulties related to their illnesses.

The Relationship Between Knowledge and Behavior in Childhood Asthma

J. L. Lauby, D. H. Rubin, L. J. Bauman

Department of Pediatrics, Preventive Intervention Research Center for Child Health and Division of Pediatric and Perinatal Epidemiology, Albert Einstein College of Medicine, Bronx, NY

Numerous educational interventions have been developed to help children manage serious ongoing illnesses such as asthma. While most programs assume that knowledge is related to initiating and/or maintaining recommended management practices, available evidence casts doubt upon the validity of this assumption for all children. We investigated the relationship between asthma management practices and (1) knowledge about asthma; (2) behavioral adjustment measured by the Personal Adjustment and Role Skills Scale (PARS); (3) anxiety; and (4) health locus of control.

Data were collected on 91 inner-city children 7 to 12 years of age with moderately severe asthma. After adjusting for age, sex, ethnic group, SES and verbal ability, asthma management practices were not significantly related to PARS, anxiety or health locus of control. There is a significant relationship between knowledge and management practices ($Beta=.32$, $p<.05$), but it is not equally strong at all levels of knowledge. Dividing the group into low and high knowledge revealed that the relationship between knowledge and management practices is strong in the low knowledge group ($B=.35$, $p<.05$), but not in the high knowledge group ($B=.14$, $p=.42$). Also, the relationship between knowledge and asthma management practices was especially strong in particular subgroups: those who scored lower on behavioral adjustment; those who had lower anxiety levels; and those who had higher internal locus of control.

These results suggest that children's knowledge about asthma can influence management practices, but only in certain subgroups. Educational interventions to children whose knowledge is already adequate may not increase adherence with recommended practices.

The Value of the Einstein Assessment of School-Related Skills in a Pediatric Clinical Setting

R. L. Gottesman, F. M. Cerullo

Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY

Children are often brought to pediatric out-patient clinics with school failure as the primary complaint. A screening instrument that could facilitate the referral process for school problems would be useful. The Einstein Assessment of School-Related Skills is a brief (7-10 minutes), individually administered screening measure designed to identify children at risk for or experiencing learning problems in grades kindergarten through 5. Previous studies using the Einstein have shown a high degree of accuracy in identifying school learning difficulties in different samples of children.

The present study explored the relationship between a child's scores on the Einstein and the ICD-9-CM Diagnostic Code given to the child based on a comprehensive interdisciplinary (ID) evaluation. In 1988, 164 English-speaking children between ages 5 and 12 seen at our center were given the Einstein during the initial interview. Subsequently, full evaluations were performed by examiners blind to the Einstein results.

The differential diagnosis following an ID team conference was compared with the results of the Einstein. Of the children diagnosed as developmentally or learning disabled according to the ICD-9-CM, 90% failed the Einstein, while 76% with other diagnoses such as adjustment reaction, conduct disorders and attention deficit disorders passed the test.

The results suggest that a child who fails the Einstein has a 90% chance of having a learning or developmental disability. The Einstein appears to be an efficient and accurate instrument for decisions regarding referrals for more comprehensive evaluations.

Neurodevelopmental Assessment of Urban, Disadvantaged Second Graders Using the Pediatric Early Elementary Examination

L. S. Grossman, M. M. Kappelman, T. Kenny, R. G. Chernoff

Department of Pediatrics, University of Maryland School of Medicine, Baltimore

Urban, disadvantaged children frequently perform poorly on standardized tests, repeat grades, are enrolled in special education programs, and leave school before graduation. Physicians often perform a neurodevelopmental assessment as part of the evaluation of these problems. The Pediatric Early Elementary Examination (PEEX) is one of few instruments available to aid in this evaluation for 7 to 9 year old children. However, this assessment tool has not been standardized in urban, disadvantaged children. This study was designed to assess the neurodevelopmental status of this population using the PEEX and correlate it with measures of school functioning.

The PEEX was administered to a random group of 249 urban, disadvantaged second graders. Two thirds of the sample were black and 93% were receiving subsidized lunches. Ability was determined using the WISC-R. School functioning was measured using the California Achievement Test (CAT), grade repetition, and enrollment in special education. Mean WISC-R total score was 97.1, both reading and math CAT mean scores were at grade level, 23% had repeated a grade, and 19% were enrolled in special education programs. On the PEEX, these youngsters did very well in the areas of gross and fine motor development. However, two or more items were in the concern range for 82% of these children in the temporal sequential area, 48% in the visual processing area, and 47% in the linguistic area. There was a correlation between the number of areas of concern on the PEEX and the WISC-R and CAT scores. However, the PEEX was not useful in identifying children experiencing school difficulties. Eighteen children (20%) with 0 or 1 area of concern on the PEEX had repeated a grade or were enrolled in special education, while 28 (44%) with four or more areas of concern had not repeated a grade or enrolled in special education.

Although urban children are more likely to have neurodevelopmental problems than suburban children, the clinician will need to be careful in interpreting the results of the PEEX in relation to school functioning when evaluating a disadvantaged, urban child.

Preschool Neurodevelopmental Testing and Reading Outcome in Grades 2 and 3

J. B. Chessare, D. Zinna, J. Joost, C. Liebich, M. Weaver

Department of Pediatrics, The Medical College of Ohio, Toledo

The identification before school entrance of children at risk for learning problems is a goal of professionals. Our study was undertaken to determine if the Pediatric Examination of Educational Readiness (PEER) and a questionnaire (ANSER system) completed by parents could predict academic outcome. Before school entrance, the study subjects were administered the PEER while a parent completed the questionnaire. The data collected were not shared with school personnel. We have previously reported on the ability of an overall PEER score to discriminate between children who were successful in kindergarten and those who were not using both placement decision and reading scores as outcome variables. Questionnaire information added no discriminating power. We now report on the ability of the PEER to sort subjects by reading scores in grades 2 and 3.

Of the original cohort of 44 children, scores on the Gates-MacGinitie Reading Tests were available for 33 (75%) who had taken the test in the spring of the second grade year and on 29 (66%) who had taken it in the spring of the following year. Study subjects were divided into two groups (high, low) with reading at grade equivalency at the time of the test as the cut point. Significant differences were found between the groups at both the second and third grades on the PEER scores (ANOVA $F = 12.42$, $p = .001$; $F = 6.07$, $p = .02$). With the PEER as the only variable in a discriminant function for classifying into the reading groups, and prior probabilities based on those within the sample, we demonstrated 85% success with second grade scores and 90% with third grade scores.

For the study population, modest increments in predictive power over pre-test probabilities were gained using the PEER. Its use may allow earlier identification of children with reading problems.

Identifying Positive Attributes in Children With Attention Deficits

D. P. Kelly, M. D. Levine, M. R. Burchinal

Clinical Center for the Study of Development and Learning, University of North Carolina School of Medicine, Chapel Hill

In contrast to the maladaptive traits typically described in children with attention deficits, many also demonstrate unacknowledged positive attributes (such as creativity) which could be advantageous to future functioning.

The revised 36-item Attention and Activity section of the ANSER System Questionnaires was used to identify a sub-group of children with attention deficits plus associated strengths. The academic functioning of this group was studied.

Questionnaires were completed by teachers and parents of 183 randomly selected students, (3 schools, grades 2-5, mean age 9.3 years, 49% male) with a mean California Achievement Test (CAT) national percentile total score of 69 ($sd = 27$).

Factor analysis of the ANSER items revealed 5 and 6 factor solutions, accounting for 71% and 63% of the total variance of the teacher and parent questionnaires, respectively. The first 3 factors for both questionnaires were similar (designated as Attention, Activity, and Behavior Factors). The fourth factor, termed the Strengths Factor, was identical for both questionnaires (12% and 14% of common variance respectively, and contained 5 items describing imagination, creativity, and similar attributes. Children were dichotomized into "Attention Problem" (AP) and "No Attention Problem" (NAP) groups based on specific criteria. Scores on the Strengths Factor were designated as "Average" (mean ± 1 *sd*), "Low" and "High" (>1 *sd* below or above mean). On the teacher questionnaire Strengths Factor, 60% of both AP and NAP children were "Average". However, 25% of the AP group scored "High" in contrast to only 15% of the NAP children ($\chi^2 = 3.68$, $p < 0.05$). Strengths scores for the AP group were positively related to their CAT scores with mean total percentile scores for the low, average, and high sub-groups being 30.8, 35.7, and 50.6 respectively. An ANOVA confirmed that scores on the strengths factor were positively associated with total CAT scores ($F(2,172) = 5.98$, $p = 0.0031$).

Findings indicate that at least one quarter of the attention deficit children in our sample showed positive attributes which were positively related to their academic functioning. Physicians who treat these children, as well as parents and teachers, need to be sensitive to these features so as to accentuate the positive and enhance self-esteem to the benefit of their long-term outcome.

Sexual Abuse: Factors Influencing Custody Decisions

P. K. Jaudes, M. Morris

La Rabida Children's Hospital and Research Center (LRCH), Department of Pediatrics, University of Chicago (Ill)

Very little is known about factors influencing the court's decision on the custody of a sexually abused child. We reviewed the charts of 138 children with proven sexual abuse admitted to LRCH between 1979 and 1987. Of these, 126 (91%) were females and 9 were males. The median age was 6.5 years, but 36 (33%) of the children were under 4 years of age. Forty one (30%) children had sexually transmitted disease (STD). The younger the child the more likely the presence of STD ($X^2 = 18.61$, $p<0.001$). 12 children who were developmentally delayed were infected with STD. Fifty five (40%) children were ultimated placed in homes other than the ones in which abuse occurred. The children who gave an initial outcry of sexual abuse were over twice as likely as others to have a change in disposition (odds ratio = 2.7, $p<0.02$). Unrelated to the decision to remove the child from the home were: the child's age; the presence of STD; developmental delay; the relationship of the perpetrator to the child; whether the perpetrator lived in the home; the presence of physical abuse and/or previous history of sexual abuse of the child. To examine whether the decision for change in custody was influenced by cumulative presence of 5 factors—STD, repeated sexual abuse, physical abuse, identification of perpetrator and perpetrator's access to the home—we constructed a risk index. There was a trend towards custody change as the risk index value increased but the trend was not statistically significant ($X^2 = 6.2$, $p>0.3$). There was no evidence of temporal change in custody decisions over the study period. These data suggest an absence of any discernible guidelines in court's decision concerning custody of a sexually abused child.

Effects of Early Carrying of Premature Infants on Cognitive Development

D. Wagner, E. Anisfeld, N. Cunningham

Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY

The study investigated an intervention with low SES premature infants that was hypothesized to promote better cognitive and social development. Mothers and their premature infants were randomly assigned to an intervention group or a control group. The intervention group mothers were given soft baby carriers and carried their infants in them while in the hospital and following discharge. The carrying began as soon after 1500 grams as the infant's medical condition allowed. The control group mothers were given the usual instructions re handling and care of their infants. A fullterm control group was recruited at 6 months to obtain baseline data. They knew nothing about the premature infants' intervention.

There were three groups of subjects: preterm (PT) intervention ($N = 17$), PT control ($N = 14$), and fullterm (FT) control ($N = 12$). The PT infants weighed between 1000 and 2000 grams at birth.

Infant cognitive and psychomotor development were assessed at 7 and 12 months corrected age with the Bayley and the Fagan Visual Recognition Memory Test. The PT intervention group performed significantly higher than the PT control group on the Bayley MDI at 7 and 12 months and on the Bayley PDI at 7 months. At 7 months, the PT intervention group mean scores did not differ from those of the FT control group. On the Fagan test, the same trend is evident, but the differences do not reach significance because of the large variance in the scores of the PT control group.

In sum, the intervention of carrying a premature infant in a soft baby carrier from an early age seems to have had a positive impact on the infant's cognitive development up to 12 months corrected age.

The Effects of Social Support on the Parturition of Primigravidous Mothers

J. M. Pascoe

Department of Pediatrics, University of Wisconsin, Madison

Earlier reports from Guatemala and Texas suggest that the constant presence of a supportive companion for primigravidous mothers during labor may be of great benefit. We studied 127 consecutive women referred to one of two community-based "birth companion" programs in Michigan to ascertain the potential effects of social support during parturition for this midwestern sample. In addition, the birthing records of 55 mothers from a community without a "birth companion" program were studied (total sample = 182).

Chart review forms were similar to those used in the Texas report, facilitating comparison of the data. Three chart reviewers (two nurses and a medical student) were trained by the author until they reached reliability. Because the caesarean section rate was highly dependent on the community, this analysis focuses on primigravidous mothers with vaginal deliveries of single infants ($n = 61$). The Statistical Analysis System was used to perform t-tests and step-wise multiple regression.

There were no differences in duration of labor among mothers who received constant support during parturition from relatives, friends, or "birth compaions"; therefore, all mothers with constant support ($N = 54$) were combined for analysis. Seven primigravidous mothers received no support during labor. The following variables were almost identical for the "support" and "no support" subgroups: maternal age, education, weight gain during pregnancy, gestation and infant birthweight. However, unsupported mothers had much longer labors (1022 ± 229 vs 589 ± 53 minutes $p = 0.01$). Step-wise multiple regression was then performed using several biological (eg cervical dilation at presentation-CDP) and demographic (eg maternal education) variables to identify those variables which explained the most variance (EV) in duration of labor. The model included: Race (EV = 15%), Support (EV = 7%), Marital Status (EV = 4%), and CDP (EV = 6%). All were significant at $p<0.05$.

These findings are similar to those reported from Guatemala and Texas and suggest that the presence of a constant companion can dramatically shorten parturition for primigravidous mothers.

The Use of a Perinatal Risk Inventory to Predict Developmental Outcome in the High Risk Neonates

A. P. Scheiner

Department of Pediatrics, University of Massachusetts Medical Center, Worcester

The goal of the study is to improve our ability to identify prior to discharge from the NICU those infants who are at high risk for subsequent developmental disabilities. The hypothesis of the study is that infants who will demonstrate developmental sequelae can be identified on the basis of a perinatal evaluation using perinatal risk factors weighted for severity.

The study was a prospective survey using a newly developed Perinatal Risk Inventory (PRI). Infants were sequentially enrolled in the study prior to NICU discharge. Each infant had to have at least one of three biologic risk factors: 1) <1500 grams or <32 weeks gestation; 2) asphyxia as defined by 3 or 5 apgars at 1 and 5 minutes; or 3) seizures and/or intracranial hemorrhage. Exclusion criteria included congenital infection, congenital malformation, severe SGA and known chromosomal abnormalities. All neonates underwent assessment using the PRI at the time of discharge. Each infant was then assessed at 9 and 18 months using the Bayley Scales of Infant Development.

One hundred and twenty seven infants were enrolled. Twenty seven have had their 9 month assessment and 100 have had both the 9 and 18 month evaluation. A score of 12 or greater on the PRI or the presence of a grade III or IV Intraventricular Hemorrhage (IVH) was considered a positive screen for subse-

quent developmental abnormalities. The data was analyzed for indexes of diagnostic efficacy using a 2×2 table. A score of 79 or less on the Bayley Mental or Motor Scale was considered suspect or abnormal. A PRI score of 12 or greater (or the presence of grade III or IV IVH) demonstrated a specificity of 91.3% and a sensitivity of 83.3%. The positive predictive value was 68.9% and the negative predictive value was 95.9%.

The high specificity and negative predictive value of the PRI may enable us to decrease the number of infants in need of developmental follow-up as well as provide parents with more specific information about developmental status at the time of NICU discharge. These preliminary findings suggest that it may be possible to identify those infants prior to discharge from the NICU who will or will not demonstrate developmental sequelae.

CLINICAL ISSUES

Influence of β-Lactamase–Producing Flora on Recovery of Group A Streptococci Following Treatment of Acute Pharyngitis

R. R. Tanz, S. T. Shulman, P. A. Sroka, R. Yogev

Department of Pediatrics, Children's Memorial Hospital, Northwestern University, Chicago, Ill

Because production of β-lactamase by normal pharyngeal flora may account for penicillin treatment failure in acute group A streptococcal pharyngitis, therapy aimed at β-lactamase-producers might decrease bacteriologic failure rates. In order to study the effect of anaerobic and aerobic β-lactamase-producers on bacteriologic outcome in acute streptococcal pharyngitis we compared 10 days of oral phenoxymethyl penicillin (P) to oral amoxicillin-clavulanic acid (AC). We used a randomized, single blind treatment protocol. Treatment failure was defined as isolation of the original streptococcal T-type 2 weeks after starting therapy. Eligible patients were 2 to 16 years old and had culture-proven streptococcal pharyngitis. 89 patients (46 AC, 43 P) were compliant with therapy as determined by urine antibiotic activity. β-lactamase-producing organisms were isolated initially from the throats of 29/46 AC and 29/43 P patients. Follow-up throat cultures 2 weeks after starting therapy were positive for group A streptococci in 7/89 (7.9%) patients; 3 had been treated with AC, 4 with P. The initial streptococcal T-type persisted (treatment failure) in 3/3 AC and 1/4 P, unrelated to recovery of β-lactamase-producers.

Our study suggests that: 1) amoxicillin-clavulanic acid is as effective as oral penicillin for treatment of acute group A streptococcal pharyngitis, but does not alter recovery of β-lactamase-producers; 2) β-lactamase production by normal pharyngeal flora may not be the only reason for failure of penicillin therapy in acute group A streptococcal pharyngitis.

Evaluation of the Efficacy of Topical Mupirocin Vs Oral Erythromycin for Treatment of Impetigo

L. L. Barton, A. D. Friedman, A. M. Sharkey, D. J. Schneller, E. M. Swierkosz

Department of Pediatrics, St Louis (Mo) University School of Medicine

Data accrued from our 2 prior investigations of impetigo demonstrated the etiologic preponderance of β-lactamase-positive *S. aureus* (SA) and comparable efficacy of systemic dicloxacillin and erythromycin. In this study, we compared the clinical and bacteriologic outcome in 97 patients with impetigo treated with either oral erythromycin (E) or topical mupirocin (M). Exclusion criteria included a history of adverse reaction to erythromycin, systemic antibiotic usage within 1 week prior to study enrollment, concurrent infection that would not be adequately treated with either of the study drugs, and concurrent administration of either Tegretol or theophylline. After obtaining a bacterial culture from a representative impetiginous lesion, the children were randomized to receive 7 days of either oral E or topical M administered 3 times daily. SA, alone, was isolated from 51% (49 of 97), group A streptococci (GAS), alone, from 4% (4 of 97) and SA + GAS in 29% (28 of 97) of patients. 14% of SA isolates were resistant to E. Of 48 children who received E, 43 (90%) were clinically improved or cured and 65% (11 of 17) were bacteriologically cured. Of 49 children who received M, 47 (96%) were clinically improved or cured, and 71% (10 of 14) were bacteriologically cured. Of patients with SA isolates 34 of 37 (92%) treated with E and 38 of 39 (97%) treated with M were clinically cured or improved. Bacteriologic cure, in the SA group, was demonstrated in 10 of 16 (63%) patients who received E and 8 of 12 (75%) patients who received M. One patient who received M developed submental adenitis. Problems associated with E were seen in 21%, and with M in 9%. At 3 week follow-up, clinical cure rates and secondary household cases of impetigo were equivalent in both treatment groups. We conclude that M is a well-tolerated, albeit expensive, alternative to E for the treatment of impetigo.

The Influence of Footwear Upon Childhood Injury

M. D. Baker, R. E. Bell

Department of Emergency Medicine, Children's Hospital of Philadelphia (Pa)

Although almost half of all injuries in young children result from falls, little information is available detailing the dynamics of these events. We prospectively studied all children injured during the months of February, May, July, and October, 1988. In addition to usual historical data, information concerning the vector of injury (i.e., loss of footing, type of footwear surface and fastener, environmental factors) was collected. Comparisons were made between those involving and those not involving loss of footing (LOF). Initial data from 2,450 injuries reveals the following:

	Sole Texture*			Type of Footwear*							Environment*		
	Rough	Smth	N/A	Bare	Snk	Shoe	Slp	Thg	Sox	Oth	Wet	Dry	Slip
+LOF	224	547	114	114	308	152	58	70	52	131	92	729	64
−LOF	841	444	280	280	892	171	66	13	40	103	32	1525	8

(*smth = smooth, N/A = bare feet; snk = sneaks, slp = footed sleep suit; thg = thongs, sox = socks, oth = other, slip = other slippery surface)

LOF occurred significantly more often in children wearing smooth sole footwear ($p<0.001$), and in injuries taking place on wet or otherwise slippery surfaces ($p<0.001$). The proportion of injuries involving LOF was lowest in barefoot children or those wearing sneakers. LOF occurred significantly more often in children wearing conventional shoes ($p<0.001$), thongs ($p<0.001$), footed sleep suits ($p<0.002$), and socks only ($p<0.001$). Body part injured was independent of footwear type, with the exception of foot injuries, which most often (58%) occurred in barefoot children. We conclude that injuries in children wearing smooth sole footwear more commonly involve LOF than those wearing rough sole footwear. These data suggest that footwear designed to improve traction might lessen the overall number of childhood injuries.

Lack of Efficacy of an Antihistamine-Decongestant Combination in Resolving Systemic Symptoms Associated With Acute Suppurative Otitis Media

J. M. Devries, R. A. Hoekelman

Departments of Pediatrics, Henry Ford Hospital, Detroit, Mich, and University of Rochester (NY) Medical Center

A clinical trial was conducted to investigate the effects on middle ear effusion and associated symptoms produced by the addition of an antihistamine-decongestant combination to the antibiotic therapy of acute suppurative otitis media (ASOM). In two suburban pediatric group practices, 243 children 7 months to 12 years old (median, 43.0 months) with ASOM were enrolled. All patients were treated with erythromycin ethylsuccinate 50 mg/kg/day and sulfisoxazole 150 mg/

kg/day. Additionally, each patient was randomized in double-blind fashion to receive either chlorpheniramine maleate 0.35 mg/kg/day and pseudoephedrine hydrochloride 4 mg/kg/day (n = 123) or placebo (n = 120). Parents completed daily symptom assessment scales on each of the ten days of medication. These scales measured activity level while awake, appetite, irritability, duration of sleep, nasal congestion, earache, ear-pulling, and overall condition. Each symptom was assessed on a 4- or 5-point scale, in which the baseline was that individual child's normal behavior.

The two groups were comparable in age, sex, race, allergy history, household tobacco exposure, concurrent upper respiratory infection, ASOM laterality, and medication reactions. According to medication diaries, 83.9% of patients in the drug group and 86.8% in the placebo group received at least 80% of both medications (p = .65). Two hundred thirty-two patients (95.5% of enrollees) completed the symptom assessment scales. The only symptom for which there was a difference in averaged ratings over the ten-day period was activity level, which was slightly more depressed in the medication group (p = .05, Wilcoxon two-sample test). Cox regression was performed to investigate the effects of several variables on the likelihood of resolution of each of the symptoms. No association with symptomatic recovery was detected for treatment assignment, medication compliance, allergy history, ASOM laterality, or resolution of middle ear effusion at the ten-day visit.

Therefore, these data fail to demonstrate any symptomatic benefit that would support the use of this antihistamine-decongestant as an adjunct to the antibiotic therapy of ASOM.

Twice-Daily Antibiotics for Acute Otitis Media (AOM) in Children: TMP-SMZ Vs Amoxicillin-Clavulanate (Amox-Clav)

W. Feldman, T. Sutcliffe, C. Dulberg

Departments of Pediatrics, The Children's Hospital of Eastern Ontario, and Epidemiology, University of Ottawa (Canada)

BID TMP-SMZ has been shown to be effective in A.O.M.; it is effective against β-lactamase producing organisms but not against group A-beta hemolytic streptococci. Amox-Clav is effective in vitro against all bacterial pathogens causing A.O.M. Amox-Clav and its parent Amoxicillin have been reported to be effective given BID for UTI, AOM, and respiratory infections in 2 European studies involving children. Given the high prevalence of A.O.M. in preschoolers, many of whom attend day-care, as well as in school-age children, a BID effective drug is highly desirable. In order to determine whether Amox-Clav's in-vitro efficacy would carry over to clinical superiority, a prospective randomized double blind controlled trial of 217 children was undertaken in a hospital walk-in clinic. Home assessment by a specially trained nurse provided 95% follow-up. Diagnosis and follow-up assessments were made by visual inspection of the tympanic membrane (T.M.) as well as with the acoustic otoscope, a hand-held instrument with high sensitivity and specificity for assessing middle ear fluid.

Randomization was successful in that there were no differences in mean age (60 months) or proportion of unilateral vs. bilateral disease in the two groups (76% unilateral). Home visits were made on days 12-16 (mean = 14), with no difference between groups. Cure was defined as normal T.M. and no fluid by acoustic reflectometry (A.R.); improvement was defined as either normal T.M. or A.R. but not both, and failure as abnormal T.M. and A.R. TMP-SMZ was associated with a cure and improvement rate of 93% vs. 82% for Amox-Clav (p = 0.03). Compliance (more than 80% of prescribed drug taken) was not significantly different. G.I. side effects were more common with Amox-Clav: vomiting (p = 0.003), diarrhoea (p = 0.001), and diaper or perianal rash (p = 0.002). There were more skin rashes with TMP-SMZ but the differences were not significant (p = 0.12). We conclude that BID TMP-SMZ is more effective clinically and produces fewer side effects than BID Amox-Clav for A.O.M.

Do Anemic Infants on Iron-Fortified Formula Need More Iron?

M. Irigoyen, L. L. Davidson, C. Seaman

Department of Pediatrics, Columbia University, New York, NY

Many infants who are fed iron-fortified-formula are screened at 6 months of age because of WIC requirements. Following current practice, infants found to be anemic (hemoglobin [Hgb] ≤11.5 g/dl), are given additional iron. To determine the efficacy of this intervention a double blind controlled trial was conducted on 336 six-months-old infants who attended an inner city hospital practice. Infants with venous Hgbs of 9-11.5 g/dl who were fed iron-fortified formula and were otherwise healthy were randomly assigned to groups receiving placebo (n = 108), 3 mg/kg/d (n = 111) or 6 mg/kg/d (n = 117) of elemental iron, to be taken for 3 months. Baseline characteristics of the three groups were not significantly different for sex, ethnicity, prematurity or entry laboratory values (Hgb, erythrocyte porphyrin [EP] or serum ferritin [SF]). Follow-up visits were scheduled for 1, 3 and 6 months after entry. At the first follow-up there were no significant differences in compliance. Attrition was comparable in all 3 groups at all visits.

	Mean Hemoglobin				Mean Ferritin			
	entry	1mo	3mo	6mo	entry	1mo	3mo	6mo
placebo	10.9	11.1	11.3	11.5	29	33	27	28
3mg/kg/d	10.9	11.2	11.4	11.4	31	36	31	31
6mg/kg/d	10.9	11.2	11.4	11.4	36	39	33	29

Multiple analysis of variance for repeated measures showed that Hgb rose in each group over time. There were no significant group differences for Hgb, SF or EP. Although almost half of the infants with entry Hgb<10.5gm/dl showed an increase ≥1 gm/dl, the proportion of responders was higher in the placebo (48%) and 3 mg/kg group (60%) than in the 6 mg/kg group (33%), (not statistically significant).

Inner city six-months-old infants with Hgb 9-11.5 g/dl, who are fed iron-fortified formula, are not iron deficient and do not respond to additional iron. Furthermore, requiring routine screening for anemia at this age is not necessary and may lead to unneeded therapy.

Diagnostic Efficacy of the Peripheral Blood Immature-to-Total Neutrophil Ratio for Bacterial Meningitis in Children

R. Lembo, D. Rubin, D. Krowchuk, P. McCarthy

Departments of Pediatrics, Yale University, New Haven, Conn, and Case Western Reserve University at Cleveland (Ohio) Metropolitan General Hospital

The ratio of immature-to-total neutrophils (ITR) in peripheral blood has been demonstrated to be useful in assessing risk of serious bacterial infection among neonates. To evaluate its diagnostic efficacy for bacterial meningitis (BM) beyond the neonatal period, we reviewed automated complete blood cell and manual differential white cell counts performed on veni-puncture samples obtained from previously well infants (age >7 days) and children suspected clinically of having meningitis who exhibited a CSF pleocytosis ($>.01 \times 10^9$ white cells/L) at the time of initial lumbar puncture. The ITR was defined as the ratio between immature neutrophils (band forms and younger myeloid series)/L and total neutrophils (segmented forms plus all immature neutrophils)/L appearing on Wright's stained blood smears interpreted by trained medical technologists.

Of 91 children studied, 24 (26%) had BM while 67 had an aseptic pleocytosis (AP). The median ITR was significantly (p<0.001) higher among children with BM (0.40) than children with AP

(0.09), whereas the median total peripheral white cell count (TPWBC) was similar among both groups (11.0×10^9/L vs 11.0×10^9/L, $p = 0.85$). An ITR >0.12 (upper limit for child age >5 days) had a sensitivity for BM of 79% (95% CI: 57-92%), a specificity of 61% (CI: 48-73%), a positive predictive value of 42% (CI: 28-59%) and a negative predictive value of 89% (CI: 76-96%). The observed sensitivity of the ITR for BM was superior to that of an abnormal TPWBC (<5.0 or >15.0×10^9/L) [46%], a CSF protein concentration >1.0g/L (61%) or a glucose concentration <2.2 mmol/L (54%), and a positive CSF gram smear (53%), and was comparable to that of a CSF total white cell count >0.5×10^9/L (79%). When combined with an abnormal TPWBC, the sensitivity of an abnormal ITR and/or abnormal TPWBC for BM was 92% (CI: 72-99%) and the specificity was 52% (CI: 38-64%).

These data indicate that the ITR alone or in combination with an abnormal TPWBC is a potentially useful adjunct for assessing risk of BM among children with a CSF pleocytosis.

Pseudomonas in Pediatric Patients With Appendicitis

I. Kaufman, G. Weinberg, J. Glaser, E. Crain

Departments of Pediatrics and Surgery, Albert Einstein College of Medicine, Bronx, NY

To prevent suppurative complications associated with appendicitis, emergency department management often includes the initiation of parenteral antibiotic therapy. Research has suggested that E. Coli and anaerobes are the most frequently isolated organisms; therefore, cefoxitin has become widely recommended for perioperative prophylaxis. The purpose of this study was to review the bacterial isolates from pediatric patients undergoing appendectomy to determine whether the choice of antibiotics is appropriate for the organisms isolated.

Forty-four patients between the ages of 14 months and 17 years in whom the diagnosis of acute appendicitis was confirmed by pathologic examination were studied during a 16 month period. Intraoperative peritoneal fluid cultures were obtained whenever possible and sent to the Bacteriology Laboratory for processing. Cultures were negative in 17 patients and for 7 patients no culture report was available. No special effort was made to isolate anaerobic species. Bacterial isolates were obtained in 20 cases (45%). Among the positive cultures, E. coli was found in 14 (60%), and Pseudomonas aeruginosa was identified in 7 (35%). Other common enteric gram negative and aerobic organisms, identified singly or in pairs, included: Enterobacter cloacae, Salmonella sp., alpha-streptococci, coagulase negative staphylococci, enterococci, diphtheroids and pneumococci. A review of the pathologic findings demonstrated that eleven of the 44 (25%) had a ruptured appendix. There was a highly significant relationship between the finding of a ruptured appendix and the presence of pseudomonas in the peritoneal culture ($p < 0.001$, Fisher exact test). Eight of the 11 patients with a ruptured appendix had a positive culture. Seven (64%) grew pseudomonas while no pseudomonas was recovered from cultures obtained from patients with nonruptured appendices.

These results suggest that children suspected of having appendicitis with perforation should receive antibiotic coverage directed against pseudomonas as part of their initial management.

Laboratory Investigation of Jaundiced Newborns: Frequency, Cost, and Yield

T. B. Newman, M. J. Easterling, E. S. Goldman, D. K. Stevenson

Departments of Pediatrics, Epidemiology, and Laboratory Medicine, University of California, San Francisco

Neonates with hyperbilirubinemia are commonly investigated with a battery of laboratory tests. We used a computerized database and medical records to study the frequency, costs, and yield of these tests in 2443 newborns weighing at least 2500 grams born at UCSF between 1980 and 1982. Four hundred forty-seven (18%) of the infants met standard criteria for "nonphysiologic" hyperbilirubinemia: the incidence varied from 9% in Blacks to 31% in Asian babies. About 55% of these 447 infants received a $100 "hyperbilirubinemia workup," including direct bilirubin, blood type and group, Coomb's test, complete blood count, reticulocyte count, and blood smear.

Coded discharge diagnoses on all 447 hyperbilirubinemic infants were reviewed. Potentially important diagnoses were confirmed by chart review. In 224 (50%) one or more possible causes of the jaundice was identified. Many such causes were apparent from history or physical exam: 78 (17%) had cephalhematomas or bruising, 31 (7%) were premature, 11 (2.5%) were infants of diabetic mothers. In 61 infants (14%), hyperbilirubinemia was associated with ABO or Rh incompatibility and in 32 (7%) with polycythemia, but it is unclear how often these were actually the cause of the hyperbilirubinemia. Twelve babies had other important diagnoses possibly related to jaundice: five had confirmed bacterial infections, three had confirmed viral infections, two had G-6-PD deficiency, and one each had hepatitis and galactosemia. In none of these twelve cases did the investigations listed above lead to the diagnosis.

We conclude that "nonphysiologic" hyperbilirubinemia is common, that the recommended tests are expensive, that they rarely lead to diagnoses that alter treatment, and that their use should be reevaluated.

Multivariate Predictive Model for Bacterial Meningitis in Febrile Children

R. Lembo, D. Rubin, D. Krowchuk, P. McCarthy

Departments of Pediatrics, Yale University, New Haven, Conn, and Case Western Reserve University at Cleveland (Ohio) Metropolitan General Hospital

To improve the ability of clinicians to assess risk of bacterial meningitis (BM) in young febrile children, we developed a predictive model for BM employing 4 independent variables: height of fever, meningeal signs, impression of toxicity and the ratio of immature-to-total neutrophils (ITR) in peripheral blood. The model was developed using a logistic regression technique on 148 febrile children, 24 of whom had BM, 62 aseptic meningitis, and 62 either a culture-proven or probable bacterial infection in the absence of meningitis. Data for each variable were abstracted from medical records. Impression of toxicity was quantified retrospectively using a scoring system based on 3 items (level of consciousness, color, hydration) and entered in the regression equation as a summary score (range: 3 [non-toxic] to 15 [highly toxic]). Meningeal signs were entered as a binary variable (any sign present/all signs absent). Fever (°C) and the ITR were entered as continuous variables. The regression equation was then used to calculate a numerical probability (i.e., risk) of BM for each patient (range: 0%-100%).

The 4 variable logistic model was a statistically significant predictor of BM ($\chi^2 = 57.0$, $p < 0.001$; $R = 0.611$). If a numerical probability of 1% were used as a cut-off value demarcating high risk of BM, the model had a sensitivity for BM of 96% and a specificity of 22%. If the probability cut-off were 10%, then the model had a sensitivity of 88% and a specificity of 80%. The ability of the model to differentiate between patients with and without BM, as assessed by computing the area (c) under the receiver operating characteristic curve which plots the rate of true-positive vs false-positive classifications at different numerical probabilities, was high ($c = 0.885$; perfect differentiation: $c = 1.00$) and was superior to toxicity ($c = 0.82$), meningeal signs ($c = 0.78$), the ITR ($c = 0.72$), or temperature ($c = 0.67$) alone.

We conclude that this multivariate predictive model which amalgamates clinical and laboratory data readily available to pediatricians has potential applicability for objectively assessing risk of bacterial meningitis in febrile children.

In Utero Exposure to Cocaine: The Risk of SIDS

H. Bauchner, B. Zuckerman, M. McClain, D. Frank, L. Fried, H. Kayne

Division of Developmental and Behavioral Pediatrics, Boston (Mass) City Hospital

An increased risk of sudden infant death syndrome (SIDS), with rates of 39-151/1000, among infants exposed to cocaine in utero has recently been reported. However, these studies have methodological limitations because of small sample sizes and lack of control groups. This study assesses the risk of SIDS, in a large prospective cohort of infants, whose mothers used and did not use cocaine during pregnancy.

Women were enrolled during registration for prenatal care and interviewed once during pregnancy and again within two days after delivery. Urine was obtained after both interviews and assayed for metabolites of cocaine. The infants were examined by study physicians. Cocaine users were identified by either self-report or a positive urine assay. To identify cases of SIDS, the list of study infants was checked against the logs of the Mass Center for SIDS.

The 996 women who were enrolled were predominantly young (34% <20), minority (87%), single (94%) and poor (78%—income <$1000/mth). 175 (17.5%) used cocaine during pregnancy—67 (38%) reported weekly use, 67 (38%) monthly use and 41 (23%) denied use, but had a positive urine assay. The women who used cocaine were more likely to use opiates (15% vs 2%, $p<.001$), smoke cigarettes (86% vs 35%, $p<.001$) and consume alcohol (81% vs 55%, $p<.001$) during pregnancy than the women who did not and their infants were more likely to be low birth weight (14% vs 8%, $p<.05$). At the time of the MCSIDS registry check, the infants were at least 8 months of age, except for 45 who were between 6 and 8 months. One infant exposed to cocaine in utero died from SIDS (5.6/1000) compared to 4 nonexposed infants (4.9/1000). The relative risk for SIDS among infants whose mothers used cocaine during pregnancy compared to those whose mothers did not use cocaine is 1.17 (95% confidence interval: 0.13, 10.43).

We conclude that the risk of SIDS among infants exposed in utero to cocaine is appreciably less than previously reported. The magnitude of the risk for SIDS approximates that found among infants whose mothers did not use cocaine, but have similar health behaviors and sociodemographic characteristics.

Who Takes Care of the Sickest Children?

M. Irigoyen, M. Goldstein

Department of Pediatrics, Columbia University, New York, NY

Patterns of service and utilization were compared in a pediatric faculty practice and a residents' continuity clinic at a university hospital. A bilingual patient survey was conducted among 600 randomly selected mother-physician pairs, 300 at each practice site. Seventy seven percent of the patients were Hispanic, 82% were on welfare, and 72% of the households were headed by women. The patients seen at the faculty practice were younger (48%<1yr, $x=2.12$ yrs) than the patients seen at the residents' clinic (29.1% <1 yr, $x=4.02$ yrs), $p<.05$. Of greater importance, however, a significant difference was found in health status: patients followed by residents were sicker than those followed in the faculty practice, as rated both by their mothers and physicians (mother's rating of child's health: 5% fair/poor in the faculty practice vs 17.6% in the resident's clinic, $p<.001$, correlation with physicians' rating = .36, $p<.001$).

Patients overwhelmingly identified the assigned pediatrician in both settings as the regular provider of care (95% in faculty practice, 96.3% in residents' clinic). However, there was a greater reliance on other sources of pediatric care among patients of the residents' clinic: 8.9% of the faculty practice patients acknowledged having another "regular" doctor compared to 21% in the residents' clinic. It is unclear whether this is due to enhanced availability of physicians in the faculty practice, poorer health status among patients in the residents' clinic or a previously established relationship with other providers in the community.

The cause in the disparity in age and case mix was determined to be administrative in origin. The majority of the patients followed in the faculty practice were referred from the well baby nursery (67.8%) (ER 3%, inpatient 2.6% and NICU 1.9%). In contrast, patients followed in the residents' clinic originated primarily from other sources (ER 34%, inpatient 12.3%, NICU 8.6%, well baby nursery 20.3%). Furthermore, an analysis of health status by source of referral revealed that the sickest children were assigned from the NICU (18.75% had fair/poor health), followed by the inpatient (11.1%) and the ER (10.1). Patients assigned from the well baby nursery were the healthiest (6.4% fair/poor health).

These institutional practices have the effect of assigning the sickest children to the least experienced doctors. Our results clearly highlight that source of assignment determines case-mix. This selection leads to major differences in age distribution and health status in patient populations and has major teaching and service implications.

EMERGENCY PEDIATRICS AND CHILD ABUSE

Legal Proof of Child Sexual Abuse in the Absence of Physical Evidence

A. R. DeJong, M. Rose

Department of Pediatrics, Thomas Jefferson University, Philadelphia, Pa, and Philadelphia District Attorney's Office

Clinicians testify in courtrooms that physical evidence of injury, sexually transmitted diseases and seminal fluid is frequently absent in cases of child sexual abuse. Legal decisions often support this clinical opinion. To determine the frequency and significance of physical evidence in legally "proven" felony cases and to assess factors related to legal outcome, a 12 month prospective study was done of felony child sexual abuse court cases.

All 115 criminal court cases involving charges of penetration prosecuted in one year were reviewed and abstracted, and 87 (76%) had resulted in conviction of the perpetrator on felony charges. Charges of vaginal rape were made in 88 cases, and oral and/or anal sodomy in 67 cases. Perpetrators were relatives in 55 and acquaintances in 50 cases. Victims ranged in age from 1.5 to 17 years (mean 10.1), and most victims were female (82%).

No significant difference in rate of felony conviction was found in cases with or without physical evidence of injury, sexually transmitted diseases, or seminal fluid. ($p=.40$) Sixty-seven of 85 cases (79%) without physical evidence resulted in felony convictions while 20 of 30 cases (67%) with physical evidence resulted in felony conviction. The child's age or sex, the type of sexual contact, the relationship of the perpetrator to the victim, the number of victims or perpetrators involved per case, the duration of the abuse, the interval from the time of disclosure to the trial, the type of trial held, and testimony by either the examining or an expert physician were not shown to effect the legal outcome of the cases.

Of cases resulting in felony convictions, physical evidence was present in only 23% (20 of 87) while physical evidence was present in ⅓ of acquittals and misdemeanor convictions. This prospective study supports the hypothesis that legally "proven" cases usually have no physical evidence. Although no consistent factors appear related to the legal outcome, "proof" of child sexual abuse appears to depend on the effective collection, preservation, and presentation of "verbal" evidence. These results should be helpful to both the clinician in counseling the family of the victim and the attorney who prosecutes child sexual abuse cases.

Accuracy of Assessments in Child Sexual Abuse

R. M. Brayden, W. A. Altemeier III, P. Siegel, P. M. Speck

Department of Pediatrics, Vanderbilt University, Nashville, Tenn, and Memphis (Tenn) Rape Crisis Center

Accurate assessment of physical findings for Child Sexual Abuse (CSA) is medically and legally important. This study 1) determined accuracy of clinicians for rating Colposcopic Photographs (CPs) and 2) identified predictors of accuracy. Fifty-one physicians and 26 nurse practitioners completed a questionnaire to access CSA knowledge. Participants were asked to rate 6 CPs for degree they suggested sexual abuse on a 7 point scale (1 = not at all; 7 = highly suggestive). Ratings by a professional with extensive experience were used as a standard. Participants were divided by level of involvement in CSA exams: Group A = supervise clinical diagnoses in CSA program (n = 3), group B = conduct exams in CSA programs with supervision (N = 34), and group C = none or occasional office exams (N = 40). Accurate diagnoses (defined as ±1 from standard) scores were found in 83% of A; 46% B; and 38% C measures. Inaccurate diagnoses (defined as >4 from standard) were found in 0% A, 16% B, and 24% C. A>B>C> differences were significant ($F<.05$) by ANOVA. Correlates for degree of agreement with standard scores were group ($r.40, p<.001$), knowledge of female perineal anatomy ($r.39, p<.001$), number of past colposcopic exams ($r.34, p=.002$), and self perceived competence in CSA exams ($r.24, p=.035$). Total exams and knowledge of sexually transmitted diseases were not significant predictors of accuracy. Stepwise regression analysis demonstrated 24% of variance for agreement with standardized scores was due to group (Beta.31) and knowledge of anatomy (Beta .29); PIN .05. The study suggests that accuracy of interpretation of colposcopic photographs is highly dependent on experience in CSA programs. Our results suggest the need for 1) the development of clinical decision-making standards and 2) supervision of medical trainees in forensic child sexual abuse examinations.

Is Childhood Sexual Abuse (CSA) Really Increasing in Prevalence? An Analysis of the Evidence

W. Feldman, E. Feldman, J. Goodman, P. McGrath, R. Pless, L. Corsini, S. Bennett

Departments of Pediatrics, Psychology, and Social Services, Children's Hospital of Eastern Ontario, Ottawa, Canada

A recent study of the epidemiology of C.S.A. concluded on the basis of analysis of 2 studies, one performed in the 1940's, and the other in the 1970's, that C.S.A. is becoming more prevalent. As part of a larger overview of the C.S.A. literature, we have analyzed data from all the prevalence studies reported in the English language over the last 10 years. In this report, we compared data obtained in the 1970's and 80's with those of the 1940's to determine if in fact C.S.A. is increasing. Using predetermined methodologic criteria for 1) the quality of the information 2) commonality of definitions of C.S.A. and 3) research design, we reviewed 17 prevalence studies: inter-rater reliability of reviewers was at least 90% for each paper. In spite of differences in study designs and populations surveyed, where definitions of C.S.A. were similar, there was striking similarity in the reported prevalence rates comparing the 1940's with the 80's. If exhibitionism is excluded and the upper age of the child is set at 13 years, all but one study give prevalence rates comparable to those of Kinsey in the 1940's, i.e. around 12%. The one exception, giving a prevalence rate of 28% suffers from a 50% response rate. Although we have no data on prevalence of C.S.A. amongst 14-17 year old girls from Kinsey's work, more recent studies show heterogeneous rates in this age group: from 6% to 42%. This variability may be due to difficulties in applying a common definition amongst studies to this age group, e.g. is sexual activity between a 16 year old female and a 22 year old male necessarily sexual abuse? Although many child protection programs, including our own, are reporting more clinical cases of C.S.A., it is likely, given the evidence from the studies we have reviewed, that C.S.A. is *not* increasing but, in a new social climate, more children and their families are coming forward for help.

Depth to Obtain a Clear Lumbar Puncture in Children Under 2 Years of Age

L. D. Kaye, D. Suskin, D. M. Super

Department of Pediatrics, Case Western Reserve University, Cleveland, Ohio

In order to define guidelines for performing a lumbar puncture that avoids puncturing the epidural venous plexus, 21 patients who presented with clinical indications for lumbar puncture were enrolled into the study. All lumbar punctures were done at the L3-4 interspace with the patient in the left lateral position. The needle was advanced in increments of 1-2 mm, until spinal fluid was draining from the needle. After collecting the fluid, the needle was marked at its point of insertion through the skin and withdrawn. The distance from the tip of the needle to the mark was measured using a spinal manometer calibrated in increments of 2 mm. Only lumbar punctures done successfully on the first attempt and producing fluid with less than 10 red blood cells/cc are reported.

The patients' age, weight and depth for obtaining clear spinal fluid, were 7.7 ± 6 months, 7.3 ± 2.9 kg, and 16 ± 2 mm (mean ± SD), respectively. In a stepwise multiple regression analysis, with weight and age as independent variables, weight correlated best with the depth of inserting the spinal needle ($r = 0.668$, $p<0.001$), and the derived linear equation predicting depth of insertion of the needle with its 95% confidence interval is: [depth of insertion (in mm) = (0.46 mm/kg) (weight in kg) + (12.64 ± 3.5 mm)].

We conclude that there is a direct linear relationship between the weight of a patient and the depth of needle insertion in order to obtain clear spinal fluid. In order to prevent a traumatic spinal tap from inserting the needle too far, we recommend that once the needle is inserted to the depth calculated from the lower limits of this formula [ie.: depth = (0.5) (weight) + 9], the needle be advanced until spinal fluid is obtained or until the upper limit of the 95% confidence interval is reached (ie. a further 7 mm). If no spinal fluid is obtained after the third attempt, the needle may be carefully advanced beyond the upper limit.

Abbreviated Cerebrospinal Fluid Analysis in Selected Pediatric Patients

L. E. Rodewald, K. A. Woodin, P. G. Szilagyi, D. A. Arvan, K. R. Powell

Departments of Pediatrics and Pathology and Laboratory Medicine, University of Rochester (NY) School of Medicine and Dentistry

The standard evaluation of cerebrospinal fluid (CSF) to rule out bacterial meningitis in children consists of cytologic and chemical analysis, gram stain, and bacterial culture. We hypothesized that if the CSF cell count is less than 6 nucleated cells per cu.mm. and no bacteria are seen on a gram stained smear, tests other than bacterial culture are unnecessary. This combination of gram stain and cell count becomes a "CSF screen" (CSFS). 5,484 CSF analyses from the Strong Children's Medical Center in Rochester, NY were reviewed to determine whether the CSFS results could be used to decide which CSF samples to analyze completely. Samples from infants admitted on the day of their birth (1,774) or containing more than 1,000 RBC/cu.mm were excluded; 3,107 samples remained. The age range was 0 to 3 years, the mean age was 33 weeks. Medical record review of positive CSF cultures confirmed the diagnosis of bacterial meningitis in 105 patients.

The CSFS demonstrated the following operating characteristics against the gold standard of confirmed bacterial meningitis:

negative predictive value 99.9% (95% CI 99.5%-99.9%); sensitivity 98.1% (95% CI 91.6%-99.7%); specificity 73%; and positive predictive value 10.9%. Two patients with meningitis had a normal CSFS, but their CSF glucose and protein concentrations and differential WBC counts were also normal. Receiver operating characteristic curve and logistic regression analyses of the 3,107 samples demonstrate that, compared with the CSF WBC count, the glucose and protein values add little additional information.

It may be possible to reduce costs by using an abbreviated CSF work-up consisting of cell count, gram stain, and bacterial culture in selected patients having a normal CSFS. At this time, implementation of an abbreviated analysis may be appropriate if conducted in the setting of a controlled clinical trial.

Reliability of Physical Signs of Meningitis in Children With Meningitis

M. P. Donahue, N. A. Schonfeld

Department of Emergency Medicine, Children's Hospital of Los Angeles (Calif)

Common teaching holds that signs of meningeal irritation such as neck stiffness on flexion and the Kernig and Brudzinski signs are not reliably found in infants with meningitis. Older children with meningitis are expected to exhibit these signs reliably. To investigate the association between signs of meningeal irritation and the presence of meningitis we carried out a prospective study on patients who underwent a lumbar puncture (LP) in the Emergency Department (ED) of Childrens Hospital of Los Angeles.

All children undergoing an LP were eligible. The ED attending physician examined each child who was to receive an LP and recorded the results.

Over a 1 year period 515 patients 0 months-18 years old were enrolled (mean 16 months). 101 patients had meningitis (mean age 29 months), 44 bacterial and 57 aseptic. Discomfort on neck flexion ($p = .0001$), and a positive Kernig ($p = .0001$) or Brudzinski sign ($p = .0001$) each correlated with the presence of meningitis. The Brudzinski sign demonstrated a 31% sensitivity and 95% specificity for meningitis. It had a positive predictive value (PPV) of 61%, and a negative predictive value (NPV) of 85%.

For children <18 mos old the sensitivity of one or more of the above three signs for meningitis was 47%, specificity 82%, PPV 36%, NPV 88%. In children older than 18 months the sensitivity of one or more of the signs was 79%, specificity 53%, PPV 43%, NPV 87%. Six out of 28 patients older than 24 months with meningitis had no signs of meningeal irritation; 38 of 73 patients <24 months old with meningitis had none of these signs positive.

The presence of signs of meningeal irritation may be helpful in diagnosing meningitis. The absence of signs of meningeal irritation at any age does not rule out the diagnosis of meningitis.

Prediction of Bacteremia Based on Temperature and WBC

D. Jaffe, G. Fleisher

Children's Memorial Hospital, Northwestern University Medical School, Chicago, Ill, and The Children's Hospital, Harvard University Medical School, Boston, Mass

Bacteremia occurs in 3-5% of febrile infants (3-36 mos). 20% of bacteremic children may develop complications, including meningitis. The purpose of this study was to quantify more precisely the utility of the previously identified risk factors of temperature (T) and leukocytosis in predicting bacteremia.

As part of a study of use of oral antibiotics for children with possible bacteremia, 955 children age 3-36 mos., with rectal T≥39.0°C, seeking care at either of 2 urban pediatric emergency departments had blood drawn for culture (BC), and 885 for WBC. 27 had bacteremia. Various combinations of T and WBC were selected to construct receiver-operating-characteristic (ROC) curves by plotting sensitivity vs. false positive rate (1-specificity).

All 27 bacteremics had T≥39.0; 20 had T≥39.5; 14 had T≥40.0; 4 had T≥40.5; and none had T≥41.0. Each increment of 0.5°C lead to a corresponding decrease in sensitivity of approx. 25%. All 26 bacteremics who had WBC done had WBC≥5000; 24≥10,000; 17≥15,000; 10≥20,000; and 6≥25,000. ROC curve analysis showed that, in screening for possible bacteremia, cutoff values of T≥39.0 and WBC≥10,000 optimized sensitivity vs. specificity (92% and 43% respectively). 368 of the 885 BC could have been eliminated (expendable). Only 58 BC were expendable with a WBC cutoff of 5000, although there was a corresponding increase in sensitivity to 100%. Using a cutoff of T≥40.0 and WBC≥15,000, 789 BC were expendable, but overall sensitivity also dropped to 35%: 65% of the bacteremics escaped detection.

We conclude: 1) Raising the cutoff for temperature leads to unacceptable decreases in sensitivity for bacteremia screening. 2) Using a WBC cutoff of ≥10,000 increases the specificity with a minimal decrease in sensitivity. 3) ROC analysis allows purpose-based refinement of selection criteria by individual clinicians.

Hyperpyrexia in Children: A Case Controlled Study

G. Alpert, E. Hibbert, G. R. Fleisher

Department of Emergency Medicine, Children's Hospital, Boston, Mass

Hyperpyrexia [temperature (T)≥41.1 C] has been reported, in children, to carry an increased risk of bacteremia (≥15%) and meningitis (10%). To test the hypothesis that hyperpyrexia is a risk factor for serious bacterial illness, we retrospectively reviewed our emergency room records. 60 children 3-36 mos. old with T≥41.1 C were identified over a period of 2 years (group 1). These index cases were compared to control children presenting with T of 39.1−40.0 C (group 2), and 40.1−41.0 C (group 3). A control patient was selected as the first child in the appropriate age and temperature range appearing after an index case in the log books. The three groups were comparable in age (mean 16 mos.), sex (male 52%), white blood cell count (WBC) (mean 14,650 mm^3) and prior antibiotic therapy (18%). Blood cultures and lumbar punctures were performed at the same frequency in all the groups. Chest X-rays, WBC counts, and urine cultures were done more frequently in the hyperpyrexic children (table). None of the hyperpyrexic children had bacteremia or meningitis. The results of chest x-rays and cultures are presented in the table.

Group	1	2	3	P
Number	60	60	60	
Bacteremia	0 (51)	2 (44)	4 (37)	0.07
Meningitis	0 (16)	0 (9)	1 (7)	0.50
Bacteruria	4 (28)	2 (15)	0 (16)	0.28
Pneumonia	8 (29)	3 (11)	2 (17)	0.40

( ) number in parenthesis = number cultured or x-rayed

Discharge diagnoses in hyperpyrexic children included otitis media (40%), viral syndrome (10%), pneumonia (13%), and urinary tract infection (5%), and did not differ from the discharge diagnoses in the other groups. 5 patients in group 1 were admitted (3 and 4 patients in the other groups). 50 patients in group 1 were started on new antibiotic treatment, significantly more than in group 2 (36 patients $p = 0.007$) but not in group 3. We conclude that the risk of bacteremia, meningitis, and other significant bacterial infections is not increased in children with T≥41.1 C.

Radial Head Subluxations

J. E. Schunk

Division of Emergency Medicine, Children's Hospital of Los Angeles (Calif)

Radial Head Subluxation (RHS) ("nursemaids elbow") is a common injury which if recognized can usually be successfully

reduced by the primary physician. This study investigated the epidemiology and clinical presentation of RHS, and compared two methods of reduction.

Children seen in the Emergency Department (ED) with RHS were eligible for study. The physician completed a data sheet and was requested to reduce the RHS with wrist supination followed by elbow extension on even days and wrist supination followed elbow flexion on odd days.

During a 9 month period 87 episodes of RHS in 83 children (mean age of 27 months with range from 4.5 to 73 months) were studied. A history of prior RHS was present in 26.7% of the children. The left elbow was involved more than the right (60.2% vs 39.8%). The chief complaint of "not using the arm" and a pull mechanism of injury was present in 61.2% and 50% of the cases respectively.

Physical examination noted the child in no distress in 85.7%, the elbow flexed slightly (<45 degrees) in 81%, pain with supination in 66.2%, and no swelling in 97.5% of the cases. After reduction, use of the arm returned in <10 minutes in 86% of the episodes. Slow return of use of the arm (>10 minutes) was not correlated with delay from time of injury to visit to the ED but was significantly associated with age younger than 24 months ($p<.01$). The initial supination-flexion maneuver had a success rate of 80.4% (41/51) compared to 68% (17/25) for the supination-extension maneuver ($p>.10$).

RHS is seen in children <5 years even without an identified pull mechanism. The child usually is not using a slightly flexed arm and has pain on supination. Slow return of the use of the arm is associated with age <24 months. The success of the two reduction techniques was not significantly different.

Selecting Extremity Injuries for X-ray: New Method for Protocol Development

K. M. McConnochie, K. J. Roghmann

Department of Pediatrics, Rochester General Hospital, University of Rochester (NY)

To assess the potential for selective x-ray use in evaluating extremity injuries, protocols were developed based on prospective observations for 617 injured children seen in our emergency department (Phase I), and tested on 603 seen one year later (Phase II). Protocols developed in Phase I performed equally well when tested on Phase II injuries. Two methods were used in developing protocols. Recursive partitioning analysis (RPA), widely used in developing decision making protocols, generated protocols for selecting upper and lower extremity injuries that would avoid x-rays for 13.6% and 32.7% of injuries, respectively, but fail to detect 5.4% and 12.8% of fractures. Logit analysis (LA), not previously used in protocol development, produced best-fitting statistical models with significant ($P<.05$) direct effects of gross signs, point tenderness, activity not routine, swelling moderate or severe, time from injury, <6 hr, and pain with motion for upper extremity; and not knee injury, activity not routine, point tenderness, and foot injury for lower extremity. For all injury types (ie, all combinations of presence or absence of these findings), risk for fracture was derived. For upper injuries, with threshold risks for fracture of 20% or 25% used to select specific injury types for x-ray, net protocol outcomes would include 18.1% or 26.8% of x-rays avoided and 5.3% or 9.2% of fractures missed. For lower injuries, using threshold risks of 10% or 15% to select injuries for x-ray, outcomes would include 25.8% or 34.0% of x-rays avoided and 5.3% or 11.7% of fractures missed. Unlike RPA, LA evaluates all clinical findings simultaneously and provides information about benefits/risks of multiple possible protocols. LA-generated protocols perform better than those generated by RPA, and they allow choice among alternative protocols based on personal values attached to benefits/risks by clinicians and patients.

Acute Iron Poisonings in Children: Evaluation of the Predictive Value of Clinical and Laboratory Parameters

N. A. Schonfeld, A. J. Haftel

Division of Emergency Medicine, Children's Hospital of Los Angeles (Calif)

Ingestion of iron containing preparations is the fifth most common toxic ingestion in children. The clinical severity is correlated with the maximum serum iron level within 4-6 hours post ingestion. Minimal toxicity is found with an iron level <300 μg/dl. Many hospitals, however, do not provide iron levels on an emergent basis. 100 hospitals with 24 hour emergency services were surveyed and only 50% could provide an iron level in less than 6 hours.

This retrospective study was undertaken to determine which readily available clinical and laboratory parameters could be used to predict the severity of an acute iron ingestion in children. The records of children who presented to the emergency department (ED) from 1978-1985 for acute iron ingestion were reviewed. 104 children were seen in the ED for acute iron ingestions. 94 children were included in the study. The ages ranged from 11 months to 6.5 years with a mean of 30 months. The most common form ingested was ferrous sulfate. Serum iron levels ranged from 38 to 923 μg/dl with a mean of 272 μg/dl.

Laboratory and clinical parameters which had statistically significant correlation ($p<0.01$) with an iron level >300 μg/dl included age less than 2 years, vomiting, white blood cell count >13,000/m3, anion gap greater than 16 meq/l and radioopaque densities on KUB. No child with zero risk factors had an iron level greater than 300 μg/dl. No child with 2 or more risk factors had an iron level less than 300 μg/dl.

The clinical and laboratory parameters of age, white blood cell count, presence of vomiting, anion gap and KUB can be used to identify the child who is at risk for a significant iron ingestion when an iron level is not readily available.

Indigent Patients Who Are Denied Care in the Emergency Department

K. N. Shaw, S. M. Selbst, F. M. Gill

Emergency Department, Children's Hospital of Philadelphia (Pa)

Recently, a primary care case management health system, similar to an HMO was formed for 100,000 indigent patients in Philadelphia. Under this system known as HealthPass, the primary care physician (PCP) assigned to each patient decides via phone call whether a child may receive care in our Emergency Department (ED) when the patient presents without prior authorization. Thus, many patients are denied access to the ED. We conducted a prospective study to learn the chief complaint and eventual diagnosis and outcome of these patients who were turned away.

Over 6 months, 588 children enrolled in HealthPass were denied care in our ED by the PCP. Almost half (47%) came to the ED during weekends or evening and night hours. The average age was 4.7 years (39% <2 years). The most common chief complaints were colds, earaches, rash, vomiting, and diarrhea; however, 9% had trauma and 10% had fever >38.2°C. All children were screened by a triage nurse; only 65% briefly by an ED physician.

Follow up was available from the PCP for 388 children (66%). Of the 60% who kept their arranged appointment, 42% received antibiotics, 3% were referred for further evaluation, and 2 children were admitted. Despite multiple attempts, follow up was available from the parents for 125 children (21%). These parents reported high compliance with seeing their PCP. No follow-up information was available for 111 children (19%). Of concern was that this group included 6% with chief complaint of trauma, 2% with temperature >39°, and 10% were less than 2 years of age.

Many indigent children who are denied care in an ED are subsequently lost to follow up and do not receive medical care, especially when the health care system relies on phone communication and accessibility of transportation. Therefore, ED's should carefully screen all children who are denied care.

PREVENTION AND EPIDEMIOLOGY

Reducing Illness in Child Care Centers

C. Lewis, C. Gilliss, R. Pantell, B. Holaday

Department of Pediatrics, University of California, San Francisco

There is increasing evidence that children in child care centers have higher rates of illness than other children. In an effort to improve child care center health conditions and thereby reduce disease transmission we developed and tested an easily exportable educational program. Twenty five child care centers had baseline data collection and then were paired and randomly assigned to have the educational intervention (experimental). Data was collected for 21 weeks. After the study was complete control centers received the educational program. The educational intervention consisted of: 1) a 15 minute videotape designed to teach about mechanisms of disease spread, reduction techniques (handwashing, diapering) and specific strategies for modifying child and staff behavior (e.g. "stop sign" reminders on faucets, handwashing songs) 2) a written health manual and symptom action guide 3) an environmental self assessment check-list and 4) health aids (e.g. sneezer belts for children). Results indicate caregivers' self-assessments of health practices were comparable pre-intervention but significantly better in the experimental group than in the control group following intervention ($t = 5.30$, $p < .0001$). Caregiver knowledge of health was significantly higher in the experimental group ($t = 3.90$, $p < .0005$) post intervention. Experimental centers showed a reduction of 9 respiratory symptom days per 100 person days from the 8 week baseline to the 13 week post intervention period while the comparable figure for control centers was a reduction of 3.6 days ($t = 2.11$, $p < .05$). The rate of gastrointestinal symptom days was too low to detect changes. The health of children in child care may be improved by improving health practices with a brief, exportable intervention.

Reduction of Infectious Disease Symptoms in Day Care Homes

A. Butz, P. Fosarelli, E. Larson

School of Nursing and Department of Pediatrics, School of Medicine, Johns Hopkins University, Baltimore, Md

Since the 1970's day care centers have been recognized as major repositories of infectious disease transmission in young children. Handwashing has been demonstrated to reduce cross-infection in day care centers. The objective of this study was to evaluate the effectiveness of certain disease prevention measures in decreasing the incidence of symptoms associated with infectious disease among 2 month to 6 year old children attending family day care homes (FDCH). We hypothesized that children attending intervention homes would have decreased symptom days of diarrhea, fever, vomiting and rhinorrhea compared to children in the control homes.

Each of 24 FDCH was randomly assigned to an intervention or control group. The intervention included both the use of disposable vinyl gloves and also the use of diaper changing disposable pads at each diaper change; both interventions were chosen to maximize any beneficial effects that might be present. The control group received neither intervention. Daily symptom records for each child were kept by day care personnel for a 12 month period. Biweekly nurse visits were made to collect diary records.

In the first nine months, one hundred thirteen children accounted for 8480 total child days. Children attending intervention homes (IH) had significantly fewer days of illnesses manifested by symptoms of fever and vomiting compared to children in control homes (CH) (fever days, IH = 69, CH = 122; $p < .001$; vomiting days, IH = 11, CH = 62; $p < .001$). Diarrhea symptoms were also reported at a higher rate in control homes than in intervention homes, but this did not reach statistical significance (IH = 77, CH = 102, $p = .09$). Days of rhinorrhea were common and were similar in both groups: IH = 627 and CH = 627.

These data suggest that the use of disposable vinyl gloves and diaper changing pads might prevent some gastrointestinal illnesses in daycare attendees, but have only a negligible effect on respiratory illnesses.

Bullets, BBs, and Boys: Understanding Gun Injuries Treated at a Pediatric Trauma Center

R. R. Tanz, M. J. Barthel

Departments of Pediatrics and Pediatric Surgery, Children's Memorial Hospital, Northwestern University, Chicago, Ill

Toy guns, nonpowder (NP) guns (BB and pellet guns), and powder (P) weapons (handguns, rifles, shotguns) all contribute to the problem of childhood gun injuries, beginning in early childhood and accelerating through adolescence. Efforts to protect children from gun injuries often fail to distinguish the impact of NP and P weapons. We undertook a review of all gun injuries treated at our pediatric trauma center since 1980 to better understand the circumstances of the shootings, the weapons used, the contribution of gun type to injury severity, and the relationship between injury severity and functional outcome. Severity was measured using the Pediatric Trauma Score (PTS) and the Injury Severity Score (ISS). The charts and x-rays of 60 patients were reviewed. Physician notes often did not describe the event and x-ray reports rarely identified projectiles found. Mean victim age was 9.6 yrs (range 0.5-15.8). 73% were male; 62% were black. 45% were injured at home, in the family car, or at the home of a friend or relative. Five (8%) inadvertantly shot themselves and 10 (17%) were shot by another child. NP guns were involved in 23% of cases, a handgun in 63%, another P weapon in 5%. In 8% the type of gun was undetermined. Patients with ISS <25 were more likely to survive without sequelae than those with ISS ≥ 25 ($p < .001$). PTS <5 was associated with death (7/12, 58%) and abnormal outcome (4/12, 33%); 24/31 (77%) with PTS >7 survived without sequelae. 2/14 (14%) NP and 6/41 (14%) P victims died. 11/14 (79%) NP and 21/41 (51%) P survived without sequelae. *Conclusions*: 1) These data confirm that NP guns are commonly involved in serious injuries; 2) ISS and PTS may aid in prognosis of gun injured children; 3) prevention is urgently needed because of the frequency of death and disability; 4) prevention will require a focus on boys, and must address children of all ages and both nonpowder and powder guns.

Attributing Cause for Unnecessary Pediatric Hospital Days Using the Delay Tool

J. D. Klein, J. R. Beshansky, H. P. Selker

Departments of Pediatrics and Medicine, New England Medical Center, Boston, Mass

Efficiency and cost containment have become primary goals of our health care system. However, there is concern that strategies for accomplishing these goals might result in non-selective reduction in both appropriate and inappropriate care. The "Delay Tool", a chart review protocol, detects, quantifies (as delays and delay days) and assigns specific causes for medically unnecessary or inappropriate hospital days for adults. In this study, we validate use of this tool in a pediatric population, describe the epidemiology of delays in a pediatric teaching hospital, and compare patterns of delay between services.

To identify "delay days", we reviewed charts of all patients hospitalized on general pediatric medicine and pediatric gastrointestinal services during a six month period. Of 354 patients, 315

charts (89%) were available for review.

All pediatric delays could be categorized by the Delay Tool taxonomy. Interobserver agreement was 96%. Ten percent of patients experienced delays. The average length of delay was 2.8 days, and delay days accounted for 5% of all hospital days. The most frequent causes of delay were test scheduling (32%), consultation (24%) and physician decision making (16%). Discharge planning and lack of appropriate outside care caused only three delays (8%); however, these accounted for a disproportionate share (23%) of all delay days. Most delays started on weekends (52%) and ended on Mondays (41%). Pediatric medical and GI services had different distributions of causes of delay ($p<.05$). Compared to adult services in the same hospital, pediatric services experienced fewer delays ($p<.01$).

The Delay Tool appears to be a useful instrument for identifying inefficiencies in health care delivery for pediatric, as well as adult, patients. Knowledge of specific delay causes should help in planning and monitoring selective reduction of inappropriate hospital utilization.

Education and Stress Management in Asthma: A Randomized Controlled Trial

J. M. Perrin, W. E. MacLean, S. L. Gortmaker, K. N. Asher

Children's Service, Massachusetts General Hospital, Department of Pediatrics, Harvard Medical School, and Department of Behavioral Sciences, Harvard School of Public Health, Boston, Mass, and Departments of Psychology and Pediatrics, Vanderbilt University, Nashville, Tenn

Children with asthma are at special risk for problems in psychological functioning, as are children with other chronic illnesses. We conducted a controlled trial of education and stress management among children ages 6-14 years with asthma. 80 children were randomly assigned to an intervention or a control group. 53 children completed the program, 30 intervention and 23 control. We examined psychological status using the Child Behavior Checklist (CBCL), children's knowledge of asthma, stress (as measured by children's life events) and daily activities before and after the intervention.

Children in the intervention group had a significant improvement in the internalizing score on the CBCL ($p<0.05$) and a significant increase in daily chores ($p<0.02$) and time playing with friends ($p<0.05$) after the intervention. Both groups, prior to the intervention, showed a significant negative relationship between stress and psychological status ($p<0.05$). The experimental group, after intervention, had no such relationship, although it was maintained for the control group. Children in the experimental group whose knowledge of asthma increased were more likely to have improvements in psychological status, in number of daily chores, and in time playing with friends ($p<0.05$).

We conclude that the intervention had a beneficial effect on psychological status and on children's daily activities. The effect may have occurred in part by decreasing the likelihood that perceived stress led to poorer adjustment.

Health Status and Adjustment: Dissecting a National Sample

R. E. K. Stein, D. J. Jessop, A. Leon

Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY

Earlier analyses of two large scale national surveys, the Health Examination Survey (HES) Cycles II ($N=7119$) and III ($N=6768$), produced higher estimates of chronic physical conditions (25% of 6-11 yrs and 35% of 12-17 yr olds) compared to the 10-15% estimated by other community-based surveys. The analyses also provided evidence of significant adjustment difficulties among youngsters with such conditions. An unusual feature of the two data-sets is that they include data from both a screening physical examination and a parental health history.

We examined whether higher estimates that we previously reported were a result of having combined the parental and physician data, and whether adjustment patterns were related to source of report of health status. Comparison of the two sources indicates striking differences in who is classified as chronically ill. There is agreement by parents and physical examinations on illness in only 4% of each survey. When estimates of chronic conditions are based exclusively on parental report, the most common method in large scale surveys, the HES Cycle II identifies 11.4% of the children and III identifies 11.6% of the youths as having a chronic illness. However, using physician assessment based on the screening physical examination, the numbers are 15.6% and 22% respectively in the two cohorts. Surprisingly, classification as chronically ill based on physical examination, rather than the parental report, correlates with the higher rates of adjustment difficulties on educational, psychological, and social variables, even though data used to evaluate these variables were obtained from parents, teachers, or the youths, rather than from the physicians.

These findings point to the strength of designs that include both clinical and interview data. They also raise questions about the relative validity of sources of information about child health status and the possibility that different techniques identify discrete subsamples.

Parent Attitudes and Practices of Children as Pedestrians

F. P. Rivara, A. B. Bergman, C. Drake

Harborview Injury Prevention and Research Center and Departments of Pediatrics, Epidemiology, and Biostatistics, University of Washington, Seattle

There are very little data on parents' expectations of their child's pedestrian skills. This study, consisting of a survey questionnaire, was undertaken to provide information on current parent attitudes and practices which could be used to guide preventive programs.

The survey consisted of 2464 questionnaires from parents of children in Gr. K-4 in a suburban school district. Although 94% of parents did not believe that 5-6 year olds can reliably cross streets alone, one-third of parents allowed Gr. K children to cross residential streets alone and Gr. 1 children to walk alone to school. The presence of speeding traffic or the lack of safe places to walk did *not* influence parents to limit their children's crossing: 25% of parents let children cross busy streets in neighborhoods where traffic speed was dangerous compared to 20% of parents in neighborhoods where speed was safe.

Most parents perceived the risk of child pedestrian injury to be less than that of MV occupant or bicycle related injury, but greater than that from drowning or fires. Educated parents were more likely to have accurate perceptions than those with less than a high school education. Few (17%) parents believed that children should be taught not to cross alone; one-half of parents, including 41% of parents of Gr. K children believed children should be taught to cross busy streets without traffic lights.

The study indicates that parent expectations for their children's pedestrian skills may be inappropriate and may be a fruitful target of injury prevention programs.

Coping Strategies to Stress in Children With Juvenile Rheumatoid Arthritis

A. L. Olson, J. Pope, R. B. Klein

Department of Maternal and Child Health, Dartmouth Medical School, Hanover, NH

The focus of many prior studies of children with chronic illnesses has been on what problems exist, not what effective coping mechanisms are utilized. This study enabled children with Juvenile Rheumatoid Arthritis (JRA) to identify the coping mechanisms

they used for common stressful events and compared them to a normal population. 34 children, 8 to 17 years (mean 12.7 yrs.), attending summer camp for JRA completed a semistructured questionnaire previously developed by J. Brown that assessed coping strategies for the stressful events of; 1) dental injection, 2) an oral class presentation and 3) an event they chose as personally stressful. Our study added the stressful event of blood drawing. Primary coping styles were determined as either positively adaptive or catastrophizing. This group was compared to a normal population of 487 children. Questionnaires were repeated two mos. later by a random 1/3 of the group with no significant change in coping found.

Overall, children with JRA were twice as likely to use positive coping mechanisms (75% vs 36%). For each type of stress children with JRA coped considerably better. Positive coping mechanisms for the personally stressful event were used by 85% of the JRA population (44% by normals). Analysis by age groups showed that more children with JRA used more positive self talk, task orientation and effective problem solving methods and made less use of attention diversion. In addition they used these mechanisms at younger ages and with both health and daily life stressors. We also investigated variables of disease severity, duration, SES, and extent of camp experience.

This preliminary study shows the impact of chronic illness may not always be negative and children can develop more effective coping strategies to stress than normals.

Findings From a Self-Administered Screening Form to Assess the Onset of Breast-feeding

J. M. Seacat, M. R. Neifert, S. M. DeMarzo

Lactation Program, Women's Hospital at AMI St Luke's, Denver, Colo

Although the majority of contemporary American women elect to breast-feed, many experience early breast-feeding difficulties. Few studies have prospectively screened for early breast-feeding problems, nor associated their presence with subsequent lactation performance.

We administered a 13-question, quick screening form to 147 mothers who were seen at 4-7 days post partum as part of a large prospective study of the onset of lactation. Intervention was offered for all detected breast-feeding problems, and a second visit occurred at 9-14 days. Maternal lactation was deemed sufficient when an exclusively breast-fed infant achieved an average weight gain of $\geq$28.5 Gm/d between the two visits. Infants gaining <28.5 Gm/d returned for a third visit at $\leq$21 days of age, at which time a final assessment of maternal lactation performance was made.

51% of mothers identified two or more breast-feeding problems on the screening form. The most frequently reported problems were: infant nursing $<8\times$/d (22.0%); infant appearing hungry after most feedings (21.1%); infant having difficulty latching-on or sustaining suckling (20.8%); mother experiencing severe nipple pain (12.4%). In spite of this prevalence of reported problems, 89% reported that breast-feeding was "going well". None of these problems was associated with final lactation outcome in this group of women who had intervention available to them.

Only the questions regarding infant elimination patterns were associated with lactation outcome at three weeks. Failure of the infant to have yellow "milk" stools by the first visit was significantly associated with subsequent lactation insufficiency ($p<0.001$). Having fewer than 4 "good sized" bowel movements each day ($p=0.003$) and voiding fewer than 6-8 times each day were also associated with subsequent insufficient lactation ($p=0.02$).

We cannot speculate whether women would have achieved the breast-feeding success rate without intervention. We hypothesize that abnormal infant elimination patterns may be present in those infants with the most compromised milk intakes and/or whose mothers have non-remediable breast-feeding problems.

Does a Pediatrician's Attire Impact Differently on Parents and Children?

P. Narula, R. Marino, W. Rosenfeld

Department of Pediatrics, Winthrop-University Hospital, Mineola, NY

To evaluate their perceptions of pediatricians based on attire 25 children (5 male and 20 female ages 5-15 years) and 25 parents (5 male & 20 female) attending an out-patient pediatric facility were shown five full figure photographs of the same physician dressed differently (1. Short white coat and tie. 2. Scrub shirt with a short white coat. 3. Shirt and tie but no white coat. 4. Long white coat and tie. 5. Shirt with no tie or white coat). A questionnaire with a series of positive (i.e.—competence, friendliness, concern, and gentleness) and negative (i.e.—incompetence, unfriendliness, lack of concern, and lack of gentleness) attributes was completed by each subject, matching the picture with the corresponding description. Positive and negative responses were added for each picture and the data analyzed (Chi Square).

Parents had a strong positive preference for the physician dressed in the short white coat and tie ($P=0.008$). In contrast the children had no positive preference for any attire. Parents least preferred attire #5 (no coat, no tie; $P<.001$). Again children did not respond negatively on the basis of dress. When parents were asked to select the doctor their child would most prefer 64% chose #1, while only 8% of the children made this selection. Eighty-four percent of the parents least preferred picture #5, but only 48% of the children agreed. This study demonstrates that a pediatrician's attire has more influence on the parents than it has on their children. Practitioners should be aware of these findings in deciding how they wish to dress.

Parenting Stress in Physician Families

J. R. Sande, R. D. Olsen, G. P. Olsen

Department of Pediatrics, Mayo Clinic, Rochester, Minn

Medical practice confers some unique demands and stressors which may affect not only physicians but family members as well. Physicians' personality factors and marital relationships have received considerable attention, however, parenting in physician families has not. This study was designed to:

1. assess parenting stress in physicians' spouses;
2. compare levels and sources of stress in resident and staff families;
3. determine if parental stress is identified during the well child visit.

Sixteen staff and 26 resident families who had well-child visits during the study period participated. Groups were controlled for physician sex (all male), family size, maternal employment and child temperament.

All spouses completed the Abidin Parenting Stress Index immediately prior to the well-child visit. The M.D./PNP who conducted the visit (blinded to PSI results) rated parental stress as observed during the visit. Home interviews to delineate factors contributing to stress were conducted by blinded interviewers.

Results: Stress levels as measured by the PSI were similar in resident and staff spouses (2 sample t-test, p's>0.10). In both groups, 12% of spouses had markedly elevated stress scores. Elevation of scores in certain subscales indicated increased stress in relation to: marital relationship, maternal health, social support, and role satisfaction.

A majority of spouses in each group described themselves as functional single parents and described limited availability of the M.D. father due to professional demands. Resident fathers were twice as likely to participate in child care when home than staff families (66 vs 30%). Seventy-five percent of resident spouses anticipated that stress would decrease after residency. However, 75% of staff spouses reported that stress levels had remained the same or increased after residency.

Parental stress was not reliably identified in the well-child visit. There was an inverse correlation between MD/PNP rating of stress and the PSI score.

Conclusion: M.D. fathers had limited time and energy for parenting, creating stress for spouses. Contrary to spouses expectations, paternal involvement in parenting, while limited during residency, tended to decrease after residency.

Can Demographic, Clinical and Psychosocial Data Predict Which Mothers Will Be Reliable in Their Clinical Judgments?

P. McCarthy, B. Forsyth, H. Bauchner, S. Sznajderman, N. Czarkowski, M. Baron, H. Fink, D. Cicchetti

Department of Pediatrics, Yale University School of Medicine, New Haven, Conn

Can demographic, clinical and psychosocial data predict which mothers will be reliable in their clinical judgments when their children have acute illnesses?

In order to address this issue, 184 mothers of infants at the 2 week well child visit were enrolled both in an inner city primary care center and a suburban private practice. At baseline, data about 11 demographic, clinical and psychosocial variables (location [inner city or suburban], age, educational level, marital status, previous children, other adults living in the home, pregnancy complications, maternal worry about outcome during the pregnancy, Spielberger State and Trait Anxiety Inventory and Forsyth Infant Vulnerability Scales) were recorded. Mothers were given routine advice about acute illnesses at scheduled well child care visits. Each time the child had an acute illness during the first 2 years of life, mothers and pediatricians in tandem and independently prior to the history and physical exam judged the chance of serious illness using a three-point global scoring system (1 = little or none, 2 = middle or moderate, 3 = high). Weighted Kappa (Kw) was used to quantitate the reliability of mothers' judgments. Pearson r correlations were performed between the 11 baseline variables, singly and in all combinations, and the reliability of judgments. Stepwise regression analysis was also performed with baseline data as independent variables and reliability (Kw) as the dependent variable.

There were 332 acute illnesses in the study children. The overall Kw, 0.26, indicated poor reliability. The multiple r correlation between the 11 variables taken together and Kw was low (0.227). No single variable had an r greater than 0.160. The r^2 for the 11 variables taken together was 0.0514. In stepwise regression only level of maternal education was a significant predictor of reliability but the r^2 for this variable was low, 0.025.

Clinical judgment is a highly specialized skill the reliability of which is not accurately predicted by demographic, clinical and psychosocial data. Thus, every parent is a candidate to benefit from teaching interventions about clinical judgment and such teaching should be offered universally.

Joint Session With APS/SPR

ADOLESCENT MEDICINE

An Analysis of Adolescent Suicide Attempts: The Expendable Child

J. Woznica, J. Shapiro

Division of Adolescent Medicine, Children's Hospital of Los Angeles (Calif)

This study empirically assessed the concept of the "expendable child" syndrome proposed by Sabbath (1969) as a contributing factor in adolescent suicide attempts. It was hypothesized that suicidal adolescents would be rated higher on a measure of "expendability" than would a psychiatric control group of adolescents with no known history of suicide attempts or suicidal ideation.

Subjects were 40 adolescents, ages 13-24, who had been seen in psychotherapy at a teenage health clinic in a large metropolitan area. Forty-five percent of the sample was male and 55% female, with a mean age of 16.9 years. Subjects were from diverse ethnic backgrounds.

All subjects were rated by their psychotherapists on suicidality and on a 12-item scale of expendability (a sense of being unwanted and/or burden on the family). Psychotherapists were blind to the nature of the study. Internal consistency of the measure was high with a coefficient alpha, of .92.

As predicted, the experimental group of suicidal adolescents (N = 20) received significantly higher ratings on the expendability measure ($p<.001$) than did the psychiatric control group of non-suicidal adolecents (N = 20). Additional characteristics of the suicidal group included runaway status and non-intact family status. Results support the concept that feeling a sense of expendability is a characteristic of suicidal adolescents. This knowledge would seem to be extremely valuable in the development of effective programs for prevention and treatment of adolescent suicide attempts. Findings suggest that further research on the expendable child concept is warranted.

AIDS and Sexual Behavior Changes in Adolescents

D. Bunch, G. Zimet, T. Anglin, R. Lazebnik, P. Williams, D. Krowchuk

Department of Pediatrics, Case Western Reserve University School of Medicine and Cleveland (Ohio) Metropolitan General Hospital

Individuals must change their sexual behavior in order to prevent the spread of AIDS. The purposes of this study were to determine whether adolescents are changing their sexual behavior based on what they have heard about AIDS, and to evaluate which factors differentiate between those who report changing their sexual behavior and those who do not. 153 urban students (grades 9-12) completed confidential questionnaires in a classroom setting. 101 (66%) indicated that they had been sexually active. The mean age of this subgroup was 17 (range 13-19). 24% of subjects were male and 85% were Black. The questionnaire included 5 indices constructed to measure: changes in sexual behavior (4 items); AIDS knowledge (22 items); AIDS beliefs matched to knowledge (22 items); social anxiety about willingness to interact with someone who has AIDS (6 items); and worries about personal susceptibility to AIDS (4 items).

Based on what they had heard about AIDS, 7% of students reported that they had ceased sexual activity, 54% had decreased their frequency of sex, 46% had had fewer partners, and 46% had increased condom use. Multivariate analysis of variance was used to determine which factors distinguished those who reported changing their sexual behavior from those who had not. Knowledge, beliefs, and social anxiety were not related to any behavior changes. However, worries about personal susceptibility were significantly greater in those reporting decreased sexual activity ($F = 10.9$, $p = .001$) and increased condom use ($F = 11.1$, $p = .001$), than in those reporting no changes.

These results suggest that some urban adolescents are changing their sexual behavior based on what they have heard about AIDS. These changes appear to be related to anxiety about personal

susceptibility. Standard educational approaches assume that increasing knowledge leads to behavior change. However, according to this study's findings, this assumption may not be valid with urban adolescents. AIDS curricula for adolescents, therefore, may need to help individuals focus on their own vulnerability to HIV infection, as well as to present factual information. In this way, realistic concern about susceptibility to AIDS may be heightened, which could lead to constructive changes in sexual behavior.

Children of School-Age Mothers: Multiproblem Adolescents

S. M. Horwitz, L. V. Klerman, J. F. Jekel

Departments of Epidemiology and Public Health, Yale School of Medicine, New Haven, Conn

Children of school-age mothers may be at increased risk for behavioral, cognitive, and emotional problems. We investigated these problems by interviewing 111 offspring born to 154 young (13-18), black, primparas enrolled in an early (1967-69) comprehensive program for school-age mothers. We located 128 (86%) of the 149 living women and interviewed 121 (95%). All of the women gave us permission to contact their offspring. Of the 121 adolescents, 2 could not be interviewed, 2 refused, 6 were not located and 111 were interviewed (92%). Information about early development was available from the original study collected at maternal program entry and at 2, 12, and 24 mos. postpartum. Data from this follow-up were collected in 90-minute semi-structured interviews and medical and educational records.

Of the 111 adolescents born to school-age mothers, 47 were female, mean age was 18, and 83% were in or graduated high school. Ninty-four percent of the adolescents were sexually active and 56 (50%) report beginning sex before age 14. Forty-one percent reported always using birth control and 25% (12 females, 16 males) have a child. Six females (8.5%) and 1 male (1.6%) met DSM-III criteria for depression, 7 males (6.3%) met criteria for alcohol abuse, and 58 adolescents (52%) report delinquent behaviors and/or juvenile. Fifty children (45%) repeated a grade in school, 71 (64%) were suspended, and 39 (35%) smoke.

Factor analysis showed clustering of 6 negative features: sex before age 14, smoking, grade retention, school suspension, alcohol abuse and no contraception. We developed an index of these 6 features (1 = present; range 0-6) and examined their relationship to delinquent behaviors and juvenile justice contacts. When 0-1 feature was present 8/36 (22%) adolescents exhibited delinquent behaviors versus 25/44 (57%; RR = 2.6) if 2-3 features were present and 26/31 (84%; RR = 3.8) if 4-6 features were present ($X^2_{LT} = 22.6$; $p < .001$). A similar trend was noted for school dropout ranging from 2/36 (5%) with 0-1 features to 11/33 (33%; RR = 6.6) with 4-6 features ($X^2_{LT} = 10.25$; $p < .01$). These relationships hold despite adjustments for family income, mothers' educational/economic success and contact with grandmothers. We conclude that negative features cluster in offspring of school-age mothers and that they predict school dropout and delinquency.

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

Needlestick Injuries Among Pediatric House Officers in New York City

S. Melzer, S. H. Vermund, S. P. Shelov

Department of Pediatrics, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY

Concerns regarding accidental needlestick injuries among house officers have increased following reports of HIV transmission via this route. The rising incidence of pediatric HIV infection in the New York metropolitan area may place pediatric house officers at particularly high risk for occupational HIV infection via needlestick injury. The present study ascertained the cumulative incidence of needlestick injury among pediatric house officers in New York City training programs who had completed at least one year of training. Two hundred ninety four house officers in eleven medical school affiliated pediatric training programs completed a questionnaire regarding needlestick injuries. Two hundred five (69.7%) had stuck themselves or been stuck with a needle contaminated with a patient's blood. In this group, five hundred eighty eight needlesticks were reported, representing an average of 2.0 needlesticks per house officer per year. Forty eight (17%) reported a needlestick involving a needle contaminated with the blood of a patient with suspected HIV infection. Only eleven of the forty eight had received counseling or HIV testing following their possible HIV exposure. These data indicate that needlestick injury among pediatric house officers in New York is common. Reducing occupational risk is an especially compelling policy issue for pediatric training programs in HIV endemic areas.

Bunk Bed Injuries

S. M. Selbst, M. D. Baker

Emergency Department, Children's Hospital of Philadelphia (Pa), University of Pennsylvania

Bunk beds are commonly used in American households, yet there are few studies regarding their safety. In our Emergency Department (ED) we conducted a prospective study to learn the incidence, epidemiology and outcome of injuries related to bunk beds. A control group of children who use bunk beds, but came to the ED for another reason, was also interviewed.

Data from 52 injured children and 58 controls have been analyzed thus far. The mean age of injured children was 4.62 years compared to the control group mean of 5.72 years ($p = 0.08$). There were 36 injured children (69%) and 30 control children (52%) less than 6 years of age ($p = 0.09$), the minimum age for bunk bed use recommended by CPSC. Of those injured, 42% had no side rails on the top bed compared to 36% in the controls ($p = 0.06$). In the control group, carpeted floors were more common ($p = 0.03$) and the ladder was more often placed at the side of the bed rather than the end of the bed ($p = 0.01$). Most injuries occurred during daytime hours, but 30% occurred between 10 P.M. and 8 A.M. Injuries occurred most often when the child fell from the top bed (54%), fell off the ladder (12%), fell off the bottom bed (10%), or the beds collapsed (6%). Injuries occurred during sleep (35%), getting in or out of the bunk bed (15%), or playing in or near the beds (35%). Of those injured while asleep, 14/18 were less than six years old. Head injuries accounted for half the trauma, and were more likely if the top bed had no side rails ($p = 0.007$). The most common injuries were lacerations (37%), and contusions (31%), but 10% had concussions and 8% had fractures. All four children (8%) admitted to the hospital fell from the top bed. Referral to a subspecialist was required in another 8%.

Injuries can be prevented if side rails were mandatory for all top beds, young children were not permitted to sleep in bunk beds, and all children were encouraged not to use the beds for play.

BEHAVIORAL PEDIATRICS

The Impact of School-Based Education on Death Concept Formation in Early Elementary School-aged Children

D. J. Schonfeld, M. Kappelman

Department of Pediatrics, Division of Behavioral and Developmental Pediatrics, University of Maryland, Baltimore

The young child's immature understanding of the concepts related to death serves to heighten death anxiety and precludes successful adjustment to loss. Little is known of the efficacy of educational interventions for young children in this area of cognitive development. This study was an attempt to determine the effectiveness of a three-week experimental school-based education program in the acceleration of death concept development in four

to eight year-old children. Children (N = 184; 54% boys, 55% Black) were randomly assigned by class to control or intervention groups. A series of six 30-45 minute presentations about concepts and affective reactions to death were provided by the principal investigator over a three week period to classes in the experimental group. The Smilansky Death Concept Questionnaire, a validated and published structured interview, was administered pre- and post-intervention phase by research assistants blinded to group assignment. Significant gains were noted for the experimental group as compared to the control group in total death concept score (gain of 4.16 vs. 1.85, $p = 0.002$; range for total score = 0-30 on instrument), total score human death (gain of 1.81 vs. 0.87, $p = 0.015$; range = 0-15), total score animal death (gain of 2.35 vs. 0.88, $p = 0.002$; range = 0-15), and two of the four factors studied, that of causality (gain of 0.86 vs. 0.11, $p = 0.0005$; range = 0-6) and inevitability and old age (1.76 vs. 0.27, $p = 0.0002$; range = 0-12). The treatment effect gain in total death concept score compared favorably to spontaneous gains expected over one year's time. An understanding of the impact of education on the rate of acquisition of these concepts has practical implications for curriculum planning in early preventive health education, particularly related to potentially fatal illness, an issue of contemporary concern.

Impact of Type and Severity of Infant Disability on Differences in Family Adaptation

J. Shonkoff, P. Hauser-Cram, M. Krauss, C. Upshur

Division of Developmental and Behavioral Pediatrics, University of Massachusetts Medical School, Worcester

Recent research on children with chronic disease suggests that severity of illness may be a stronger correlate of family adaptation than diagnosis. The validity of this hypothesis for infants with disabilities was tested in a cross-sectional analysis of baseline data from a longitudinal study of early intervention (EI) efficacy.

Child and family data were collected from mothers of 217 disabled children (Down syndrome [DS], n = 60; motor impairment [MI], n = 79; developmental delay [DD], n = 78) within one month of entry into EI services (mean age = 11.2 months). No differences were found among the three diagnostic groups in parent education, employment status, family size, or income; a higher percentage of mothers in the DS group were married. Using ANOVA procedures, no differences were found in demographics, parenting stress, or measures of social support by severity of disability. In contrast, differences by diagnostic group were found on the *Parenting Stress Index* ($F = 3.36$; $p = .04$). Post hoc Scheffe tests found that the DS group showed lower total stress scores, while the MI and DD groups showed greater stress on the Social Isolation Subscale ($p = .001$). Differences on the *Family Support Scale* were also significant, with DS parents reporting larger ($p = .01$) and more helpful ($p = .000$) support networks.

These data suggest that, at the time of EI entry, differences in parenting stress and social support are related more strongly to the child's diagnosis than to the severity of the disability. The recognizability of a specific diagnosis, and the contrasting uncertainty regarding the prognosis of non-specific disabilities, may be particularly important for early parental adjustment.

Psychosocial Problems During Child Health Supervision Visits

L. Sharp, R. Pantell, L. Olsen

Department of Pediatrics, University of California, San Francisco

An explicit goal of child health supervision visits is to gather information and provide guidance about the psychosocial problems of children and families. The purpose of this study was to determine the extent to which parents had opportunities to express psychosocial concerns and the nature of physician responses to these concerns during health supervision visits.

We analyzed videotapes of child health supervision visits by 34 children aged 5-12 years to pediatricians and family physicians. Coding systems with acceptable interobserver reliability were developed to assess: 1) the nature of opportunities provided to express concerns, 2) categories of psychosocial problems expressed by parents and children and 3) the nature of physician responses. In 88% of the child health supervision visits opportunities were created by the physician to discuss psychosocial concerns or spontaneously raised by the parent or child. Creation of an opportunity was defined as the physician asking open ended questions (48) or when specific psychosocial issues were raised (16). In half of the visits parents or children expressed a total of 30 psychosocial concerns. Psychosocial problems raised included conduct/behavior problems (47%), insecurity (13%), family, sibling or social problems (13%), learning difficulties (10%), somatization (7%) and other (10%). Physicians' response to these psychosocial concerns were as follows: 17% ignored the concern, 43% were passive—asking further exploratory questions but providing no guidance or reassurance, 3% reassured the parent, 27% responded with psychosocial information and/or action, 3% medical information and/or action, 7% a combination of these latter two modes of actions. We have documented that parents and children are given and take the opportunity to express psychosocial concerns to their physicians. Unfortunately, in 60% of cases physicians did not give guidance, information or reassurance. This study suggests the importance of further efforts focusing on the ability of physicians to effectively respond to patient's psychosocial concerns.

Abnormalities of Growth in Homeless Children

A. H. Fierman, L. M. Quinn, S. W. Shulman, C. Courtlandt, B. P. Dreyer

Department of Pediatrics, New York University School of Medicine, Bellevue Hospital Center, New York, NY

In a continuing study of the health status and growth of homeless children, we reviewed the initial visits of 427 homeless and domiciled children, birth to eighteen years, who presented consecutively to our outpatient department. The following information was collected from each record: age, sex, birth weight, gestational age, height and weight, family income level, duration of homelessness and parental drug use.

The height percentile distribution in the homeless group was skewed toward shorter values when compared to National Center for Health Statistics (NCHS) standards ($p<.001$), and to a 1:1 age and income level matched group of domiciled children ($p<.001$). Heights of domiciled children were not significantly different from NCHS standards. The weight percentile distribution in the homeless group was also skewed toward lower values when compared to NCHS standards ($p<.001$) and domiciled children ($p<.001$). In contrast, weights in the domiciled group were skewed toward higher values ($p<.001$).

Multiple regression analysis was performed to quantify the proportion of variability in height and weight percentile distributions attributable to age, sex, income level, birth weight, gestational age, parental drug use, and homelessness. After controlling for the effects of all other independent variables, homelessness was significantly correlated with lower height ($p<.05$) and weight ($p<.01$) percentiles. Parental drug use and homelessness were significantly correlated ($p<.01$). Hierarchical analysis demonstrated, however, that parental drug use did not independently account for the lower height and weight percentiles in homeless children.

Duration of homelessness did not influence height. However, children with longer durations of homelessness (>6 months) showed a trend toward lower weights. While this did not achieve statistical significance, the power to detect a difference was low (.35).

Homeless children have more extreme growth delays than other urban poor, not explained by birth weight, gestational age, or parental drug use. Longer duration of homelessness may be associated with poor weight gain.

The Effects of Early Communication Between a Provider and Mother in the Neonatal Period

J. R. Serwint, M. Wilson, A. K. Duggan, D. E. Mellits, C. DeAngelis

Department of Pediatrics, Johns Hopkins Hospital, Baltimore, Md

In a prospective, randomized clinical trial we investigated whether a post-partum visit between a mother and her infant's future continuity clinic pediatrician combined with improved telephone access would enhance identification of the pediatrician as a source of advice, increase maternal infant care knowledge, decrease maternal anxiety and post-partum depression and improve health care utilization.

Of 251 mother-infant pairs, 147 were randomized to the control group, 104 to the intervention group. The control group received routine care from the nursery staff including a follow-up clinic appointment. The intervention group received in addition 1) a visit and an educational session from the infant's clinic pediatrician approximately 24-36 hours post-partum, 2) telephone follow-up from this pediatrician 2 to 3 days post-discharge, and 3) a special 24-hour phone access number to reach a designated on-call physician during the first 2 months of the infant's life.

Outcome variables were measured by chart review and maternal interview. The intervention group mothers were more likely than control group mothers to bring their infant for a scheduled clinic visit in the first 30 days ($p = .01$), to seek some form of care at the clinic ($p = .007$), and to report having tried to reach their infant's own pediatrician by phone ($p = .001$). Differences favoring the intervention group in viewing their pediatrician as a source of advice ($p = .07$) and delaying introduction of solids past 2 months of age ($p = .06$) approached statistical significance. There were no differences between the groups in the infants' emergency room utilization, in the infants' receipt of immunizations by 90 days of age, in maternal infant care knowledge, or in maternal anxiety or post-partum depression.

Our intervention succeeded in improving some aspects of health care utilization and appeared to increase maternal identification with the infant's clinic pediatrician.

GENERAL PEDIATRICS AND PEDIATRIC EDUCATION

A Prospective Evaluation of the Efficacy of Noninvasive In-Hospital and Outpatient Management of Febrile Infants

M. D. Baker, L. M. Bell, J. R. Avner

Divisions of General Pediatrics, Emergency Medicine, and Infectious Diseases, Children's Hospital of Philadelphia (Pa)

Although it is common practice to hospitalize all febrile infants less than 2 months of age while awaiting bacterial culture results, prospective investigation justifying this approach is lacking. We studied the safety and cost-effectiveness of non-invasive in-hospital and outpatient management of well-appearing febrile infants.

All infants 29-56 days old with rectal temperatures in excess of 38.2°C presenting to CHOP were enrolled. Following a complete history, physical examination, and sepsis work-up, each child was assigned to one of three groups. In-hospital controls (IHC, $N = 95$) were those children with either laboratory or clinical parameters suggestive of serious infection. The remaining 70 well-appearing infants with normal laboratory parameters (intervention group) were randomly selected for either in-hospital observation (IHO, $N = 32$) without treatment or outpatient observation (OPO, $N = 38$) without treatment, but with repeat physical examinations at 24 and 48 hours. Diagnoses in the IHC group included: viral syndrome ($N = 34$), aseptic meningitis ($N = 29$), pneumonia ($N = 9$), UTI ($N = 8$), otitis media ($N = 7$), bacterial sepsis ($N = 3$), bacterial gastroenteritis ($N = 3$), bacterial meningitis ($N = 2$), bronchiolitis ($N = 2$), botulism ($N = 1$), and syphyllis ($N = 1$). Four of the patients had multiple diagnoses. None of the 70 patients meeting intervention criteria had proven bacterial infections. Average medical costs were: $4,225 (IHC), $2,950 (IHO), and $725 (OPO). Our data indicate that while a significant proportion of febrile 1-2 month old infants have documented invasive infections, it is possible to identify those who can be appropriately and cost-effectively managed without antibiotic treatment in either the in-hospital or outpatient setting.

Inpatient (I) Versus Combined Inpatient/Outpatient Therapy (CIO) of Serious Infections in Children

K. A. Woodin, C. J. Davis, D. K. Bauserman, A. P. Higgins, J. A. McMillan, K. R. Powell

Departments of Pediatrics and Preventive Medicine, University of Rochester (NY), and Pediatrics, State University of New York Health Science Center, Syracuse.

Long-acting antibiotics like ceftriaxone make it possible to consider CIO for serious bacterial infections. We hypothesized that patients (pts) receiving CIO consisting of therapy in hospital followed by once daily intramuscular injections at home would not differ from those receiving I in medical outcome but would have a significantly shorter hospital stay.

Hospitalized children receiving parenteral antibiotics for >48 hrs during 8/87-8/88 were identified. Pts with conditions that would make CIO inappropriate were excluded while those expected to require hospitalization to complete a proscribed course of parenteral antibiotics were eligible for study. Pts enrolled in Rochester (R) received CIO while pts in Syracuse (S) received I. Participants kept daily expense and symptom diaries. Questionnaires and telephone interviews were completed to assess physician acceptance and medical complications.

CIO was considered inappropriate for 127(46%) of 275 pts receiving parenteral antibiotics in R and 186(59%) of 315 pts in S. There were 51(19%) and 55(18%) in R and S respectively excluded because continued parenteral antibiotics were not needed. 31(32%) pts eligible for CIO in R (CIO group) and 18(24%) in S (I group) participated in the study. Infections included meningitis (CIO 12; I 4), osteoarthritis (CIO 6; I 9), bacteremia (CIO 6; I 1) and other (CIO 12; I 4). There was no significant difference in the mean days of parenteral antibiotic therapy (CIO 14.8; I 17.8, $p = 0.26$). There were no treatment failures. Complications of therapy were similar except for more mild diarrhea in the CIO pts ($p < 0.001$). The mean duration of hospitalization was significantly less for the total group of CIO pts (7.1 vs 17.8, $p < 0.001$) as well as for the subgroups with meningitis (7.2 vs 12.0, $p < 0.001$), osteomyelitis (14.5 vs 27.5, $p = 0.001$) and septic arthritis (7.3 vs 23.8, $p = 0.002$).

For pts requiring hospitalization for a proscribed course of antibiotics, equivalent medical outcome can be achieved by supervised CIO with a significant reduction in length of hospitalization.

Predictors of Pneumonia in Infants Less Than 12 Weeks of Age With Acute Respiratory Infection

S. Berman, M. B. Shanks, D. Feiten, G. Horgan, C. Rumack

Departments of Pediatrics and Radiology, University of Colorado School of Medicine and University Hospital, Denver, Colo

Acute respiratory infection (ARI) during the first three months of life is an important cause of morbidity and mortality throughout the world. The usefulness of clinical findings to identify pneumonia needs further study. Sixty six infants (age 2-12 weeks) with an ARI were enrolled in a prospective outpatient study. Chest x-rays were read independently by two pediatric radiologists and were classified as negative, slight, moderate and severe. Cases with moderate or severe findings had diffuse interstitial changes and/or parenchymal densities consistent with pneumonia and com-

prised 80% of the study group. The sensitivity, specificity, predictive value, and likelihood ratio (LR) for the clinical findings are shown below.

Clinical Finding	Sensitivity	Specificity	Predictive Value	LR
Resp. rate >50	73%	23%	80%	0.95
Resp. rate >60	40%	61%	72%	1.02
Rales	26%	85%	88%	1.73
Retractions	66%	54%	85%	1.43
Wheezing	30%	69%	80%	0.97

Respiratory rate >50 was not a useful sign because of low specificity. The highest LRs were for rales and retractions. The presence of either retractions, rales, or a respiratory rate >60 identified 85% of cases with pneumonia and can be used to identify cases that should have chest x-ray and pulse oximetry. Oxygen desaturation (<88%) with pulse oximetry was the most accurate predictor of pneumonia with a sensitivity of 63%, specificity 77%, and LR of 2.7.

Improving Outcomes in Asthmatic Patients: Results of a Randomized Trial

R. Pantell, C. Lewis, L. Sharp

Department of Pediatrics, University of California, San Francisco

A number of educational programs have focused on improving the knowledge and functional status of children with asthma. Considerable time commitment is frequently required, limiting applicability. In an earlier effort we produced a brief educational intervention (8 minute videotape and accompanying written materials) which increased direct communication between children and their physicians, especially in areas concerning management and medications. The purpose of this study was to determine whether this intervention would be effective in improving outcomes in asthmatic children. Physicians in two university and eight community practices were paired on demographic characteristics and randomized; child and parent assignment was determined by physician assignment. The intervention (one each for child, parent and physician) consisted of brief videotape and educational materials demonstrating to children how to become actively involved in their medical care, asking parents to express their concerns and showing physicians techniques for cognitively appropriate communication with children. Control subjects received a similar intervention focusing on general aspects of asthma etiology and treatment. Eighty children, aged 5-15 years have been enrolled and are being prospectively monitored.

Outcomes assessed using standardized instruments included knowledge of the child's own treatment regimen, child's satisfaction with medical care and functional. Experimental children knew their medication frequency more often than controls (66% vs 43%, $p<.02$); knowledge of types of medication, names of medications, amounts of medications, and satisfaction with medical care were also higher in experimental group children, but did not achieve statistical significance. Functional status was measured 3 months after the intervention, using 5 adaptations of measures with acceptable psychometric (RAND, FSIIR) properties, and was higher for asthmatics in the experimental group for all measures but achieved statistical significance only for global health (3.2 v 2.4, $p<.025$). A brief educational intervention encouraging children to actively participate in their medical care can improve important outcomes for asthmatics.

Maternal Smoking and Childhood Asthma

M. Weitzman, S. Gortmaker, D. K. Walker, A. Sobol

Department of Pediatrics, Boston (Mass) City Hospital and Boston University School of Medicine, and Harvard School of Public Health, Boston.

A substantial literature demonstrates that passive smoking by children is associated with an increased incidence of lower respiratory illness and diminished pulmonary function. The relationship between passive smoking and childhood asthma, however, is not clear. We analyzed data from the Child Health Supplement to the 1981 National Health Interview Survey with information about 4937 children aged 0-5 to study the relationship between maternal smoking and the (a) prevalence of childhood asthma, (b) age of onset of children's asthma, (c) likelihood of taking asthma medication, (d) number of bed days in the past year, and (e) number of hospitalizations among children with and without asthma.

Multivariate logistic regressions controlling for sex, race, family income, maternal education, family size, and number of rooms reveal an odds ratio for asthma of 2.0 among children whose mothers smoke 0.5 packs of cigarettes or more per day compared to children of nonsmokers ($P=.005$). Similar analyses identified maternal smoking of 0.5 packs as an independent risk for children's use of asthma medications (O.R.2.2, $P=.001$). Multivariate analyses also indicate that maternal cigarette smoking is independently associated with an increased risk of developing asthma in the first year of life (O.R.2.0, $P=.001$ if mother smokes 0.5 packs or more per day). Maternal smoking is also associated with increased numbers of hospitalizations by its association with an increased risk of asthma as well as by contributing to hospitalizations independent of a child having asthma. There was no evidence that maternal smoking is associated with increased numbers of bed days or hospitalizations among children with asthma.

These results indicate that maternal cigarette smoking is associated with higher rates of childhood asthma, an increased likelihood of using asthma medications, an earlier onset of the disease, and increased hospitalizations, but not with increased bed days or hospitalizations among children with asthma. Thus it appears that maternal smoking is associated with an increased risk of asthma among children aged 0-5 years, but these data do not support the contention that maternal smoking results in increased morbidity among children with asthma.

Patterns of Crying in Colic: Implications for Etiology

M. A. Geertsma, J. S. Hyams, B. Bernstein, N. Etienne

Departments of Pediatrics, St Francis Hospital, Hartford Hospital, University of Connecticut Health Center, Hartford and Farmington, Conn

Past studies of colic have not investigated different patterns of infant crying. This prospective study identified two distinct patterns of crying that are disturbing to parents and have potentially different etiologies.

Parents of 110 newborns were instructed on completing a 24 hour cry log which recorded characteristics of crying including number of crying episodes (frequency) and duration of crying (inconsolability). 2-4 day records were obtained at 2-4 weeks and again at 6-8 weeks preceeded by questionnaires assessing parental attitudes about the baby including adaptation to the infant, satisfaction with the infant, and opinion about the infant's cry.

Two distinct clinical patterns were identified, frequent cry infants (FC), and highly inconsolable infants (HI). Consistent with the incidence of spontaneous office complaints about colicky crying, and to further explore these groups, FC infants were defined as >1 S.D. above the mean for frequency of cry and HI were defined as >1 S.D. above the mean for inconsolability. Remaining infants were labeled noncolicky (NC). Highly inconsolable infants did not cry frequently ($p<.001$) and frequently crying infants were not highly inconsolable ($p<.0029$).

Univariate ANOVAS for each parental attitude rating showed differences between the FC, HI, and NC infants at both 2-4 and 6-8 weeks ($p<.0021$ to $<.001$).

Both FC and HI ratings were more negative than NC for all three parental attitude measures ($p<.05$) at 2-4 weeks. However, by 6-8 weeks, while HI ratings remained more negative, FC ratings were not worse than NC infants, suggesting adaptation to frequent crying.

We conclude that two distinct patterns of infant crying disturb parents. One pattern, FC, may be reflective of sleep variability. The other, HI, may be more consistent with true pain. These findings support multiple etiologies in colic, including organic causes of pain and also variable parental interpretation of and response to infant crying. They further help explain past research disagreement on etiology and treatment in studies using less discriminating definitions of colic such as retrospective parental impressions or arbitrary amounts of total crying per day.

Can Every Woman Breast-feed?: The Incidence of Early Lactation Insufficiency

S. M. DeMarzo, M. R. Neifert, J. M. Seacat

Lactation Program, Women's Hospital at AMI St Luke's, Denver, Colo

Based on maternal reports, the leading cause of early discontinuation of breast-feeding is "insufficient milk". The high prevalence of inadequate milk supply contrasts with the widespread assertion that "every woman can breast-feed," provided they have adequate motivation, information, and support.

This report describes early findings from a prospective study of 177 healthy, motivated and well educated, primiparous women and their term, healthy breast-fed infants. Women were enrolled during the last trimester of pregnancy, and had access via telephone or pager to a Child Health Associate with expertise in lactation management.

Women and their nursing infants were seen twice in the first two weeks post partum. Naked infant weights were obtained at each visit using the Sartorius integrating balance. Breast-feeding was evaluated at each visit, and specific intervention was prescribed for detected breast-feeding difficulties. The most common intervention was the use of the piston electric breast pump to augment infant suckling, relieve breast engorgement, or to heal extremely sore nipples. Maternal lactation was deemed to be sufficient when an exclusively breast-fed infant achieved an average weight gain of $\geq$28.5 Gm/d between the two visits. Infants gaining <28.5 Gm/d returned for a third visit at $\leq$21 days of age.

Despite high maternal motivation and education, availability of professional support, conscientious breast-feeding management, and early intervention for detected breast-feeding problems, 29.4% of healthy primiparous women delivering term, healthy infants were unable to achieve infant weight gain of at least 28.5 Gm/d between two visits in the first two weeks. The incidence of breast-feeding problems was significantly higher among women with lactation insufficiency than among women with adequate lactation ($p<0.001$). With continuing intervention, 61.5% of women with initially inadequate lactation were able to achieve lactation sufficiency by three weeks post partum, while 11.3% of the study participants had persistent insufficient lactation.

We are currently examining multiple biologic, behavioral, and psychosocial factors to investigate their association with maternal lactation performance.

Analgesic Use in the Emergency Department

S. M. Selbst, M. Clark

Emergency Department, Children's Hospital of Philadelphia, and Medical College of Pennsylvania, Philadelphia

The relief of pain is one of the most common reasons for seeking care in an Emergency Department (ED), yet pain may be inadequately treated in the ED for a variety of reasons. We conducted a retrospective chart review to see if children received analgesic treatment similar to adults with the same acute, painful conditions. Data from 113 patients have been analyzed thus far.

Charts of 52 children from the ED of Children's Hospital of Philadelphia (CHOP), and 61 patients from the ED of the Medical College of Pennsylvania (MCP) were reviewed (41% of these were age $\leq$19). Ages ranged from a few months to 88 years (mean 16.7 years). There were 52% males, and 80% were black. All patients had acute pain due to sickle cell crises (18%), lower extremity fractures (19%) or 2° or 3° burns (63%). The mean length of stay in the ED was 2.42 hours, and 9% required hospitalization.

In the ED, 62% of patients with painful conditions received no pain medications at all and only 34% got narcotics. Children (age $\leq$19 years) were much less likely to receive pain medications ($p=0.00005$) or narcotics ($p=0.00006$). Children seen in the adult ED of MCP were no more likely to get analgesics than those at CHOP. Senior citizens (age $\geq$65 years) also got fewer analgesics (not significant). When narcotics were used in the ED, only four patients (no children) were underdosed. Upon discharge from the ED, 62% of all patients had no pain medications prescribed. Children were less likely to receive analgesics at discharge, but this was not significant ($p=0.08$). Pediatricians and ED physicians are reluctant to use analgesics, especially narcotics, for children in pain. This may be due to fear of complications, inability to recognize pain in children or ignorance about analgesia. The data suggests ED physicians need further education about management of acute pain.

Parental Presence During Medical Procedures

K. A. Merritt, J. R. Sargent, L. M. Osborn

Department of Pediatrics, University of Utah School of Medicine, Salt Lake City

In the last two decades parental participation in child health care has dramatically increased. Although the trend is toward encouraging parents to be more involved, the attitudes of parents and health care workers regarding inclusion or exclusion of parents during medical procedures has rarely been explored. The present study surveyed 115 pediatricians and pediatric housestaff, 63 pediatric nurses, and 78 parents in the Salt Lake City area regarding their attitudes and experiences with respect to parental presence during medical procedures.

Philosophically, two thirds of the pediatricians reported a permissive attitude toward parental presence during procedures, but housestaff were more likely to report a restrictive attitude ($p=.03$). The vast majority of pediatricians indicated that they allow parents to be present during routine procedures, but are less likely to allow them during more invasive procedures, irrespective of the age of the child. Sensitivity to consumer desires was suggested by the physicians' report that parental factors more often influenced their decision to include parents than doctor or child-centered factors. Consistent with pediatricians, nurses expressed a permissive attitude toward parental presence during routine procedure. During invasive procedures, inpatient nurses would be less likely to permit parents than either outpatient nurses or pediatricians. Although physicians reported otherwise, nurses perceived that pediatricians encourage parental presence due to child-centered factors and exclude parents based on potential interference with the procedure.

Parents confirmed the pediatricians' report of inclusion of parents during a variety of procedures. Only with x-ray studies were parents as likely to be excluded as included. Similar to nurses, parents perceived that pediatricians would encourage parental presence primarily for the comfort of the child and secondarily for parental reasons. Although only 2% of parents felt they would be too upset to benefit their children during a procedure, a majority believed pediatricians would exclude them for fear of parental overreaction or interference.

These results indicate a consensus among parents, nurses and pediatricians in permitting parental presence during routine medical procedures, but greater diversity in attitude and practice for more invasive procedures. Although pediatricians reported a permissive philosophy based upon parental factors, both nurses and parents emphasized child comfort as the critical determinant of parental presence.

'Night People': Pediatric Emergency Department Utilization During the Night

L. M. Pachter, S. Ludwig

Division of General Pediatrics and Emergency Medicine subdivision, The Children's Hospital of Philadelphia (Pa)

Many pediatric housestaff and ED personnel have the opinion that a great number of pediatric ED visits during the late hours of the evening are made by families that have no consistent source of continuing care, are undertaken at that time for the caretaker's convenience, and are in many instances, "inappropriate". This study was undertaken to better define the nighttime ED user in regards to the social, demographic, familial, and illness related factors that enter into the decision to seek care.

A questionnaire was administered to those caretakers who presented to our pediatric ED between the hours of 11 p.m. and 7 a.m. Questionnaire dimensions included demographics, social/familial factors, medical, and visit related factors. Also recorded were the triage assessment of severity of illness, patient age, sex, method of payment, and waiting time before being seen by a physician. A control group consisting of caretakers who presented for care for their children between 7 a.m. and 5 p.m. were also given the questionnaire.

The questionnaire was completed by 170 nighttime utilizers and 202 daytime controls. Nighttime users were more likely to have private physicians, were ill for shorter periods of time, were more likely to attempt treatment at home prior to arriving at the ED, tended to use the ED more often, and spent their days outside of the home (in schools or daycare), as compared to the daytime controls ($p<0.05$). The average waiting time was longer during the night than during the day (7 a.m. to 5 p.m.). There were no differences in caretaker age or education level, nor number of parents in the household. The prime reasons for presenting for care during the night (as well as during the day), according to the caretaker, were illness concerns and not those of convenience.

GENERAL PLENARY

Carrying as Colic 'Therapy': A Randomized Controlled Trial

R. G. Barr, U. A. Hunziker, S. J. McMullan, H. Spiess, D. G. Leduc, J. Yaremko, R. Barfield, T. E. Francoeur, P. Rossy

Department of Pediatrics, Montreal (Canada) Children's Hospital

In normal infants, increased carrying can reduce crying by 40% at 6 weeks (*Pediatrics* 1986, 77:641). To determine if it was effective as a therapy for colic (crying seen as a problem by parent and physician), 47 infants with colic (5 to 32 days of age) from 3 Montreal and Atlanta practices entered a randomized controlled trial. The trial compared standard advice (be responsive to crying, check diaper, pacifier, etc.) to standard advice + "supplemental" carrying (increase carrying *in addition to* that which occurs in response to crying). Parent interventions and 6 infant behaviors (including cry/fuss) were recorded weekly during baseline (pre-randomization), immediately post-intervention, and at 6, 8, and 12 weeks of age. Mothers used previously validated diaries and were blind to the study hypothesis.

Overall carrying increased 77% (6.3 vs 3.5 hr/day) and "supplemental" carrying 97% (4.5 vs 2.3 hr/day) in the experimental group (all $p<.005$). Cry/fuss duration (3.5 vs 3.5 hr/day) and frequency (8.6 vs 9.6 episodes/day) were similar in standard and supplemental groups during baseline (both $p>.10$) and then gradually declined to 12 weeks. However, there was no difference in duration immediately post-intervention, or at 6 or 8 weeks (std. vs supp.: 2.9 vs 3.0, 2.7 vs 2.9, 2.3 vs 2.3 hr/day respectively). At 12 weeks, standard infants actually cried less (1.2 vs 1.9 hr/day; $t=2.2$; $p<.05$). Other measures (cry/fuss frequency, cry and fuss duration and frequency) showed similar patterns. Probability of having missed a 25% improvement in the supplemental group was 22%.

Conclusions: Compared to standard advice to be "responsive", supplemental carrying does not further reduce cry/fuss in infants with colic. This apparent resistance to increased carrying (in marked contrast to normal infants) may be a defining feature of colic.

Bicycle Helmet Use by Children: Evaluation of a Community-Wide Helmet Campaign

C. DiGuiseppi, F. Rivara, T. Koepsell

Harborview Injury and Prevention Research Center and Departments of Pediatrics, Epidemiology, and Health Services, University of Washington, Seattle, Children's Hospital National Medical Center and Department of Child Health and Development, George Washington University, Washington, DC

To evaluate a community-wide bicycle helmet campaign, we observed children riding bicycles at sites randomly selected within high, middle and low income census tract strata in Seattle (intervention city) and Portland, Oregon (control city) before and 4, 12, and 16 months after the campaign's start. A total of 9871 children were observed, with similar proportions seen in the 2 cities and 4 observation periods. Helmet use increased from 5.5% before the campaign to 15.6% afterward in Seattle, and from 1.0% to 2.9% in Portland. Completed analysis from the first 3 observation periods revealed strong associations between helmet use and nonwhite race (OR, 0.4; 95% CI, 0.3, 0.7); geared bicycles (OR, 2.2; 95% CI, 1.6, 2.9); riding at parks (OR, 1.9; 95% CI, 1.2, 3.0) or on bicycle paths (OR, 3.5; 95% CI, 2.1, 5.7); and riding with helmet-wearing children (OR, 31.2; 95% CI, 19.4, 50.2) or adults (OR, 41.0; 95% CI, 25.5, 66.0). The proportions of helmet wearers adjusted for these confounders were 5.6% in Seattle and 0.8% in Portland before the campaign, and 11.1% and 2.4% respectively one year after its onset, a statistically significantly greater increase in use in Seattle than in Portland ($p<.01$). Essentially all of the difference between Seattle and Portland in change in helmet use from baseline occurred in the low and middle income strata. We conclude that a community-wide bicycle helmet campaign can significantly increase helmet use among children, especially in lower income areas.

Is Childhood Obesity Protective or an Added Risk Factor for Adult Hypertension? A Study Over 50 Years

J. H. Strauss, E. Charney

Departments of Pediatrics, Fallon Clinic, and the University of Massachusetts Medical School, Worcester

Obese children are more likely to become obese adults who, in turn, are more likely to have hypertension. However, in 1971 a 40 year, non-concurrent, prospective study from Hagerstown, Maryland, reported an increased risk of hypertensive vascular disease with adult but not childhood onset obesity. Further, children who stayed overweight over the 40 years had the same risk of hypertension as did the non-obese. Those findings implied that childhood onset obesity poses significantly less risk for adult hypertension than does adult onset obesity and may even be protective.

We sought to replicate the hypothesis that the risk of hypertension will be higher in adult than childhood onset obesity in a retrospective, case-control study. School age heights and weights back to 1925 were available from the Philadelphia school system. Overweight and obese adults were chosen by review of all charts from four internal medicine practices in Philadelphia. Patients age 50 to 66 years, with 3 documented blood pressure measurements (off medication), and without diabetes or renal disease were selected. Eligible patients were sent a questionnaire to ascertain

where they went to school: 64% had attended school in Philadelphia between 1927 and 1955. School height/weight data were available on 147 (70%); 110 for ages 5-8, 121 for ages 8-12, and 139 for ages 13-16. Seventy-six had hypertension (cases) while 71 were normotensive (controls). Child and adult weight status was calculated both by relative weight percentile and body mass index (BMI).

For both overweight and obese adults, the distribution of childhood weight status showed no significant differences between the hypertensive and normotensive populations. Controlling for sex, using different childhood ages, and using either weight status measure did not produce any increased risk of hypertension as hypothesized.

These data suggest that amongst obese and overweight adults the risk of hypertension is not influenced by the age of onset of the obesity: adults who have been obese since childhood appear to be at no greater risk for hypertension than those whose obesity begins after childhood.

Social and Environmental Risks for Childhood Asthma

M. Weitzman, S. Gortmaker, D. K. Walker, A. Sobol

Department of Pediatrics, Boston (Mass) City Hospital and Boston University School of Medicine, and Harvard School of Public Health, Boston.

Unlike a number of childhood problems, such as low birthweight, infant mortality, and lead poisoning, it is not clear that there are racial or socioeconomic disparities in the prevalence of childhood asthma. In fact, the prevalence of asthma in various populations, and factors related to differential rates of occurrence are still largely unknown. We analyzed data from the Child Health Supplement to the population based 1981 National Health Interview Survey with data about 15,416 children to address the following questions: (a) Are there racial, socioeconomic, or other characteristics of children associated with their likelihood of having asthma? In particular, is race associated with the prevalence of asthma independent of socioeconomic status?; and (b) Are there environmental conditions that are associated with an increased prevalence of asthma?

Among children aged 0-5 years asthma is more common among those with the following characteristics: males, blacks, lower family income, lower maternal education, maternal smoking, larger family size and fewer rooms (each at $P<.01$). Multiple logistic regressions identified independent associations only of: male gender (OR = 1.7, $P=.007$), maternal smoking (OR = 2.0, $P=.005$), and family size ($P=.003$). Among children aged 6-17 years asthma is more common among males, blacks, lower income, higher maternal education, smaller family size, and fewer rooms (each at $P<.01$), whereas multivariate analyses identify independent associations only of male gender (OR = 1.6), lower income, higher maternal education, and fewer rooms (again $P<.01$ for each). There was no relationship between the prevalence of asthma and breastfeeding or urban/rural residence and race has no independent association using multivariate analyses.

We conclude that social and environmental factors exert profound influences on the prevalence of childhood asthma, that black and poor children do have substantially higher rates of asthma, and that most of the racial and economic disparity in prevalence can be accounted for by virtue of maternal smoking and several other environmental characteristics.

Parents' vs Physicians' Utilities (Values) for Clinical Outcomes in Potentially Bacteremic Children

M. S. Kramer, A. M. MacLellan, D. G. Leduc

Departments of Pediatrics, and Epidemiology and Biostatistics, McGill University Faculty of Medicine, Montreal, Canada

Our previous analyses of decision strategies in children 3-24 months with acute-onset fever ≥39°C and no evident bacterial focus of infection indicated that the risks of routine blood cultures (the unnecessary hospitalization and treatment of children who clear their bacteremia spontaneously) outweigh its benefits (the prevention of a few cases with major infectious sequelae). Because those analyses were based on parents' values for beneficial and adverse clinical outcomes, we wished to examine whether those values differed in physicians and, if so, whether the differences were sufficient to change the results of the decision analysis. Using a pre-tested linear analog utility scale, we evaluated 8 potential clinical outcomes in potentially bacteremic children by surveying 121 parents of healthy 3-24-month-old children attending a private pediatric group practice and 57 attending physicians of a tertiary-care children's hospital emergency room. Utilities were based on a 0-1 normalization, where 0 is the utility of the worst outcome (meningitis or other major bacterial infection) and 1 the utility of the best outcome (complete recovery without venipuncture or hospitalization).

Parents gave higher "disutility" (Δu) than did physicians to the discomfort of venipuncture ($\Delta u = .18$ vs .09, respectively; $P=.002$) and the development of minor infections sequelae ($\Delta u = .17$ vs .05; $P<.0001$). Physicians, on the other hand, assigned far greater disutility to major infectious sequelae ($\Delta u = .36$ vs .11; $P<.001$). Even based on the physicians' values, however, expected utilities (u_E's) favored the "no blood culture" strategy ($u_E = .9903$) over "universal blood culture" ($u_E = .8981$) or even "selective blood culture" (blood cultures only in children deemed to be at highest risk of bacteremia) ($u_E = .9822$). Moreover, the result was insensitive to feasible ranges of probability estimates. Thus physicians who routinely obtain blood cultures are not acting consistently with their own values. Unless greater benefits can be demonstrated for the test, our findings suggest that physicians should either obtain fewer blood cultures or develop less aggressive protocols for treating children whose cultures are positive.

Utilization of Health Services by Children Who Were Identified During the Post Partum Period as Being at High Risk of Child Abuse or Neglect

J. M. Leventhal, A. T. Berg, C. Brady, R. M. Garber

Department of Pediatrics, Yale University School of Medicine, New Haven, Conn

Previous efforts to identify newborns who are at high risk of maltreatment have focused on the benefits of early interventions to the children. Little is known about the use of health services by this high-risk group and whether early intervention might decrease utilization and the costs of care. Therefore, we compared the use of health services by high-risk and non-high-risk children.

114 newborns born at Yale-New Haven Hospital from 1979-1981 and identified as being at high-risk of abuse or neglect by clinicians during the post-partum period became the high-risk group (HR). For each HR infant, a comparison (NHR) was selected from the birth logs and matched on birth date, gender, race, and Medicaid status. Utilization data through the child's 4th birthday were ascertained by reviewing records at the 2 hospitals and 2 health centers.

The median number of visits per year to the hospitals' primary care centers were similar. Hospitalizations (H) for three types of conditions were examined: (1) for *medical problems*, 34% of HR vs 21% of NHR were hospitalized at least once ($p<.05$) (total number of H was 61 vs 29, respectively). (2) For *accidents*, 6% of HR vs 2% of NHR were hospitalized ($p=$ NS) (total H 7 vs 2), despite the same number of visits for accidents: HR = 117, NHR = 116. (3) *Maltreatment* (abuse or neglect) ocurred 3 times more often in the HR group; H occurred even more frequently: 7% vs 1% ($p<.05$) (total H 11 vs 1). To determine whether these differences were due to bias in who gets hospitalized, we also examined severity of the medical problems and lengths of stay. For severe (e.g. bacterial meningitis) or moderate (e.g. croup) problems, H occurred 3 times more often in the HR group (48 vs 16). The number of hospitalized days was markedly elevated in the HR group: medical problems: 327 vs 88 days; accidents: 44 vs

9; maltreatment: 265 vs 2. Finally, 32% of HR vs 5% of NHR were placed in foster care at least once ($p<.001$).

We conclude that HR children use an extensive amount of expensive services. Successful interventions for this group would not only decrease the adverse effects on the children but also substantially reduce the costs of care.

Predictors of Long-term Success Among School-age Mothers

S. M. Horwitz, J. F. Jekel, L. V. Klerman, H. S. Kuo

Departments of Epidemiology and Public Health, Yale School of Medicine, New Haven, Conn

Despite 20 years of federal, state and local funding for pregnant teenagers little is known about the long-term impact of teenage pregnancy on the young mother or her offspring and less is known about the effectiveness of intervention programs for these women and their children. We studied these issues in a 19-year follow-up of 154 black 13-18 year old primiparas who were enrolled in an early (1967-69), comprehensive, medical, social and educational program for school-age mothers in New Haven, CT. Between 6/87 and 6/88 we located 133 women (85%): 5 had died, 7 refused follow-up, and 121 were interviewed (95% of 128 living and located). Follow-up data were combined with data from the original study collected at program registration and again at 2, 12 and 24 months postpartum. Data were collected in a 90-minute semi-structured interview and medical chart abstractions.

At the time of the interview, former adolescent mothers ranged from 32 to 39 years. They were often unmarried (68%), high school graduates (71%), and economically independent (82%). Forty-eight percent earned more than $15,000. Most of the women (64%) reported many (>19) negative life events in the past year, were less than fully satisfied with their lives (60%), rated their emotional health as moderate to poor (40%) and were deeply or fairly religious (67%). Substantial proportions of mothers met DSM-III criteria for depression (13%), and for substance abuse (17%).

Overall, 62% of the former young mothers fulfilled our criteria for educational (high school completed) and economic (no welfare) success at the 19-year follow-up. Economic and educational success at follow-up were predicted by 3 features measured two years after leaving the program; no additional pregnancies and school completion or continuation (OR = 9.9), little social isolation (OR = 6.1) and a sense of control over one's life (OR = 5.2). Other predictors of success included being in 11th or 12th grade at time of pregnancy (OR = 9.6), life time fertility control (OR = 3.6) and high program participation (OR = 2.7) ($X^2 = 34$, 6df, $p<000$; tau-A = 36%). These results could not be explained by key socio-demographic variables measured 19 years ago (family welfare status, head of household, household size).

We conclude that these data suggest a complex picture of frequent clinical problems coupled with long-term educational and economic success among school-age mothers. Former adolescent mothers who actively participated in the comprehensive program and were two-year post program successes were likely to be long-term successes. These results may help identify pregnant adolescents who will need special interventions to achieve long-term success.

Improving Patient Outcomes Through Improved Communication: Randomized Controlled Trial of an Educational Intervention

C. Lewis, R. Pantell, L. Sharp

Department of Pediatrics, University of California, San Francisco

Previous research has shown that a brief educational intervention designed to promote active, competent communication during pediatric office visits significantly increased physician-child substantive communication and child-initiated communication. This study reports a second randomized trial, designed to assess whether the communication intervention would also improve patient and parent outcomes, in a sample of 139 five to fifteen year old patients having office visits for health supervision and illness care. Physicians at two university practices were paired according to demographic characteristics and one member of each pair randomly assigned to the experimental group. Child and parent assignment was determined by their physician's status. The intervention consisted of brief videotapes (one each for parents, children, and physicians) and accompanying written materials (a workbook for children and visit self-assessment for physicians) designed to increase children's active involvement in understanding and contributing to their health, physicians' substantive, developmentally-appropriate communication with children, and parents' expression of concerns early in the medical visit. Control group subjects received a comparable educational program addressing other health issues. Four visit outcomes were assessed: children's rapport with physicians; children's anxiety; children's preference for an active health role; and parents' satisfaction with the medical visit. All four were assessed using measures with published psychometric properties. Experimental group children reported significantly higher rapport with the physician (3.3 v 3.1, $p<.01$); and significantly greater preference for an active health role (2.7 v 2.5, $p<.007$). Despite greater role expectations for the experimental group there was no difference with control children in anxiety (1.1 v 1.1, n.s., 65 df). Experimental group parents reported significantly higher satisfaction with the medical visit (2.36 v 1.93, $p<.01$). These results suggest that a brief, educational intervention administered during waiting room time can positively impact physician-child rapport and parent satisfaction and increase children's preference for an active role in health.

Who Subsidizes Ambulatory Pediatric Research?

R. E. K. Stein, S. S. Kessel

Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY, and Bureau of Maternal and Child Health and Resources Development, Rockville, Md

Funding of research has been an issue of major concern to general pediatricians in academia. To explore the nature of financial support for successful research efforts, we undertook a retrospective survey of all authors of abstracts selected for presentation at the annual meeting of the Ambulatory Pediatric Association (APA) in the Spring of 1988 and prospectively collected funding data on all abstracts submitted for the 1989 meetings. None of the funding data were available to reviewers during the paper selection process.

Analyses of responses returned for 76 of the 86 (88%) presentations in 1988 indicate that the majority (51%) were conducted without direct grant funding. Work of only 22 (29%) of the presenters was fully funded (range $1,500 to $600,000) and only six projects received more than $100,000. An additional 20% of projects were partially funded. Of those 37 supported fully or in part, almost 60% were funded by governmental sources, predominantly from federal United States and foreign national funding sources. Private or foundation funding was the second most common source of support. Most projects not funded directly were conducted using institutional resources, but 10% of presentations resulted from work that was reportedly done with no funding or institutional support at all. Among accepted papers, those that reviewers ranked most highly tended to include more funded projects, but there were unfunded projects along the whole spectrum of reviewer ratings. Additional analyses will be available on all 1989 APA abstract submissions and will also examine the relationship of funding to acceptance rate on the 1989 program.

The 1988 findings suggest that much of the work presented at the annual meetings of the APA is done on marginal economic resources. Although no comparable data exist from other societies, anectodal report suggests that more research is funded and this leads us to speculate that better funding in general and ambulatory pediatrics might influence progress in these areas.

Injuries in Child Care Centers

R. Pantell, C. Lewis, C. Gilliss

Department of Pediatrics, University of California, San Francisco

There have been few longitudinal studies of injuries in children attending child care. We implemented a prospective study of injuries in 25 child care centers over 21 weeks in order to determine the nature and etiology of injuries and to test the effectiveness of an educational intervention in improving safety knowledge and reducing injuries. Using a randomized prospective crossover design, information was gathered on actual injuries as well as safety knowledge of providers in experimental (5 weeks baseline, 16 weeks post intervention) and control (13 weeks baseline, 8 weeks post intervention). The intervention consisted of written materials and safety aids. groups. A total of 926 children were at risk for 47,723 child days. Results indicated experimental group self assessment of safety practices was comparable pre-intervention, but higher than control group practices post-intervention ($t=5.3$, $p<.0001$); experimental group knowledge was also higher post intervention ($t=3.9$, $p<.005$). There was no detectable difference between experimental and control group injury rates; therefore injuries are combined to provide epidemiologic information. These were 321 discrete injuries: 18 children had ≥3 injuries in this period. Minor scrapes and bruises were most frequent (29.5%) followed by falls while running/walking (24.7%), blows from children/object (13.5%), falls from heights (12.9%) and human bites (8.5%). Serious injuries were rare (e.g. one burn); in only 7 instances was the child sent home or physician contact made. Injuries were more common outdoors, accounting for 60% of injuries. Demographic characteristics of the centers and child care providers were not predictive of injury rates. Serious injuries in child care settings were demonstrated to be rare in this study and most injuries minor and unavoidable in active young children. Intervention studies which address serious injuries will need sample sizes in excess of 1,000,000 child days or a population at higher risk to demonstrate moderate (>50%) rate reductions. As 25% of all injuries (blows, bites, etc.) were caused by other children, we recommend that safety education programs redirected to promote positive social skills in young children.

Vision Screening at Preschool Health Supervision Visits: A Collaborative Study

R. C. Wasserman, C. A. Croft

Pediatric Research in Office Settings (PROS) Network, American Academy of Pediatrics, Elk Grove Village, Ill

Vision screening is recommended as part of preschool health supervision (HS) in order to identify children with (or at risk for) amblyopia, a preventable and common cause of permanent visual loss. We studied vision screening at preschool HS visits in a large group of pediatric practices to determine whether and how children were being screened, and to identify factors associated with screening.

The PROS Network consists of pediatricians in 26 AAP chapters who have agreed to collaborate in practice-based research. PROS pediatricians are generally younger and more likely to practice in groups than the AAP membership as a whole. Over 12 weeks from May to July of 1988, data were collected on all children ages 3 through 5 seen for HS visits in 102 PROS practices, regardless of whether vision screening was to be done. Information was obtained about demographics, past history, the clinical encounter, and vision screening.

A total of 8409 children were enrolled; 28% were age 3, 35% age 4, and 36% age 5 years. Fifty-two % were male. Eighty-six % were White, 9% Black, 3% Hispanic, and 1% Asian. No vision screen was attempted in 33% of children overall—62% of those age 3, 29% of age 4, and 19% of age 5 ($p<.001$). Hispanic (56%) and Black (63%) children were less likely to have screening attempted than White (66%) or Asian (71%) children ($p<.001$). The most common reasons given for not screening were "not routine" (44%), "too young" (40%), and "screening done previously" (17%). Thirty-one % of the sample were screened for both acuity and binocular vision, and 34% for acuity alone. One third of the children had neither testing for binocular vision, nor a cover/uncover test on physical exam, and thus were not screened for strabismus. Overall, 90% of acuity tests were interpretable; tests of 3 year olds were least likely to yield interpretable results (70%). Among 3 year olds, however, hand cards gave a higher proportion of interpretable results (84%) than machines (71%) or wall charts (63%) ($p<.001$).

This PROS study identifies problems: underscreening of younger children, with ⅓ of the sample unscreened for strabismus. Solving these problems will more effectively prevent amblyopia among children who rely on pediatricians for HS.

Career Patterns of Men and Women Members of the Ambulatory Pediatric Association

R. E. K. Stein

Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY

Pediatrics is changing as a result of the increasing number of women entering medicine. The 1986 Ambulatory Pediatric Association (APA) membership survey provided an opportunity to examine how these changes in the gender distribution are reflected in the patterns of professional careers of APA members.

We analyzed 1,000 membership surveys returned anonymously by 84% of APA members. 63% of respondents were male and 37% female. As a group, women members are significantly younger, less often married, and have fewer children than men. Overall they are also significantly more likely to be part-time faculty members, have lower faculty rank and incomes, publish less, and are less likely to be principal investigators of grants. They are more likely to see either general pediatric or subspecialty patients than are male members, but less likely to combine the two. To determine the effect of length of medical career on these patterns, further analyses were performed on the 63% of respondents who indicated the date of their MD degrees. The sample was divided into three strata by MD date (pre 1965, 1965-1975, post 1975) and analyses were restricted to those with full-time (FT) faculty appointments. Only income continues to show differential patterns across all strata by gender. FT female faculty who completed their MD degrees prior to 1965 make significantly less income ($p<.0003$) than do male counterparts; women in both other groups also tend to earn less ($p=.1$). Among those who graduated after 1975, women have significantly fewer publications and are less often principal investigators, reviewers, or members of editorial boards. However, the income inequality is particularly noteworthy since by all performance indicators (i.e. publications, grants, and faculty rank), women in the two more senior strata are performing equally to their male counterparts.

These data suggest that among APA members women in FT academic careers are as productive as their male colleagues in all but the youngest cohort, but they are not always compensated at comparable levels. They raise questions about whether the younger cohort of women will remain less productive or whether their current productivity represents a temporary state that will reverse over time.

AUTHOR INDEX TO APA ABSTRACTS

Alpert, G. 424
Altemeier, W. A. III 423
Anglin, T. 429
Anisfeld, E. 418
Arvan, D. A. 423
Asher, K. N. 427
Avner, J. R. 432
Baker, M. D. 419, 430, 432
Barfield, R. 435
Baron, M. 429
Barr, R. G. 435
Barthel, M. J. 426
Barton, L. L. 419
Bauchner, H. 422, 429
Bauman, L. J. 416
Bauserman, D. K. 432
Bell, L. M. 432
Bell, R. E. 419
Bennett, S. 423
Berg, A. T. 436
Bergman, A. B. 427
Berkelhamer, J. E. 415
Berman, S. 432
Bernstein, B. 433
Beshansky, J. R. 426
Brady, C. 436
Brayden, R. M. 423
Buck, P. 414
Bunch, D. 429
Burchinal, M. R. 417
Butz, A. 426
Cerullo, F. M. 416
Charney, E. 435
Chernoff, R. G. 417
Chessare, J. B. 417
Cicchetti, D. 429
Clark, M. 434
Cloud, G. 412
Corsini, L. 423
Courtlandt, C. 431
Crain, E. 421
Croft, C. A. 438
Cucchiara, A. 414
Cunningham, N. 418
Czarkowski, N. 429
Dabrow, S. 415
Davidson, L. L. 420
Davis, C. J. 432
DeAngelis, C. 432
DeJong, A. R. 422
DeMarzo, S. M. 428, 434
Devries, J. M. 419
DiGuiseppi, C. 435
Donahue, M. P. 424
Drake, C. 427
Dreyer, B. P. 431
Duggan, A. K. 432
Dulberg, C. 420
Easterling, M. J. 421
Etienne, N. 433
Feinstein, R. A. 412, 413
Feiten, D. 432
Feldman, E. 423
Feldman, W. 420, 423
Fierman, A. H. 431
Fink, H. 429
Fleisher, G. 424
Fleisher, G. R. 424
Fleming, G. V. 412
Forsyth, B. 429
Fosarelli, P. 426
Francoeur, T. E. 435
Frank, D. 422
Fried, L. 422
Friedman, A. D. 419
Gall, M. 413
Garber, R. M. 436
Geertsma, M. A. 433
Gill, F. M. 425
Gilliss, C. 426, 438
Gilson, D. 414
Glaser, J. 421
Goldman, E. S. 421
Goldstein, M. 422
Goodman, J. 423
Gortmaker, S. 433, 436
Gortmaker, S. L. 427
Gottesman, R. L. 416
Grossman, L. S. 417
Gutgesell, M. E. 413
Haftel, A. J. 425
Hauser-Cram, P. 431
Hibbert, E. 424
Higgins, A. P. 432
Hoekelman, R. A. 419
Hoffmann, N. G. 413
Holaday, B. 426
Horgan, G. 432
Horwitz, S. M. 430, 437
Hunziker, U. A. 435
Hyams, J. S. 433
Irigoyen, M. 420, 422
Jaffe, D. 424
Jarman, F. C. 415, 416
Jaudes, P. K. 418
Jekel, J. F. 430, 437
Jessop, D. J. 427
Joffe, A. 413
Joost, J. 417
Kappelman, M. 417, 430
Kaufman, I. 421
Kaye, L. D. 423
Kayne, H. 422
Kelly, D. P. 417
Kenny, T. 417
Kessel, S. S. 437
Kittredge, D. 414
Klein, J. D. 426
Klein, R. B. 427
Klerman, L. V. 430, 437
Klevan, J. 415
Koepsell, T. 435
Koss, R. G. 414
Kramer, M. S. 436
Krauss, M. 431
Krowchuk, D. 420, 421, 429
Kuo, H. S. 437
Larson, E. 426
Lauby, J. L. 416
Lazebnik, R. 429
Leduc, D. G. 435, 436
Lembo, R. 420, 421
Leon, A. 427
Leventhal, J. M. 436
Levine, M. D. 417
Lewis, C. 426, 433, 437, 438
Liebich, C. 417
Ludwig, S. 435
Luxemburg, M. 413
MacLean, W. E. 427
MacLellan, A. M. 436
Marino, R. 428
McCarthy, P. 420, 421, 429
McClain, M. 422
McConnochie, K. M. 425
McGrath, P. 423
McLain, L. G. 412
McMillan, J. A. 432
McMullan, S. J. 435
Mellits, D. E. 432
Melzer, S. 430
Merritt, K. A. 434
Morris, M. 418
Narula, P. 428
Neifert, M. R. 428, 434
Nelson, D. B. 414
Neuderfer, J. 414
Newman, T. B. 421
O'Connor, K. G. 412
Oh, M. K. 412
Olsen, L. 431
Olsen, G. P. 428
Olsen, R. D. 428
Olson, A. L. 427
Olson, R. 414
Osborn, L. M. 434
Pachter, L. M. 435
Pantell, R. 426, 431, 433, 437, 438
Pascoe, J. M. 418
Pass, R. F. 412
Perrin, J. M. 427
Pless, R. 423
Pope, J. 427
Powell, K. R. 423, 432
Quinn, L. M. 431
Radius, S. M. 413
Rivara, F. 435
Rivara, F. P. 427
Rodewald, L. E. 423
Roghmann, K. J. 425
Rose, M. 422
Rosenfeld, W. 428
Rossy, P. 435
Rubin, D. H. 416, 420, 421
Rumack, C. 432
Sande, J. R. 428
Sanders, J. M. 412
Sargent, J. R. 434
Scheiner, A. P. 418
Schneller, D. J. 419
Schonfeld, D. J. 430
Schonfeld, N. A. 424, 425
Schum, T. R. 414
Schunk, J. E. 424
Schwartz, R. H. 413
Seacat, J. M. 428, 434
Seaman, C. 420
Selbst, S. M. 425, 430, 433
Selker, H. P. 426
Serwint, J. R. 432
Shapiro, J. 429
Sharkey, A. M. 419
Shanks, M. B. 432
Sharp, L. 431, 433, 437
Shaw, K. N. 425
Shelov, S. P. 430
Shonkoff, J. 431
Shulman, S. W. 431
Shulman, S. T. 419
Siegel, D. M. 414
Siegel, P. 423
Smith, D. E. 413
Sobol, A. 433, 436
Soileau, E. J. 412
Spear, B. A. 413
Speck, P. M. 423
Spiess, H. 435
Sroka, P. A. 419
Starr, M. C. 415, 416
Stein, R. E. K. 416, 427, 437, 438
Stevenson, D. K. 421
Strauss, J. 435
Super, D. M. 423
Suskin, D. 423
Sutcliffe, T. 420
Swierkosz, E. M. 419
Szilagyi, P. G. 423
Sznajderman, S. 429
Tanz, R. R. 419, 426
Upshur, C. 431
Vermund, S. H. 430
Wagner, D. 418
Walker, D. K. 433, 436
Wasserman, R. C. 438
Weaver, M. 417
Weinberg, G. 421
Weiss, J. 415
Weitzman, M. 433, 436
Williams, P. 429
Wilson, M. 432
Woodin, K. A. 423, 432
Woznica, J. 429
Yaremko, J. 435
Yindra, K. J. 414
Yogev, R. 419
Zimet, G. 429
Zimmerli, W. H. 414
Zinna, D. 417
Zuckerman, B. 422

PEDIATRICIANS

Infectious Disease

ARAMCO's Dhahran Health Center (DHC) in Saudi Arabia needs a Pediatric Infectious Disease Specialist to join a staff of 17 in its modern 483 bed hospital. The DHC functions as a referral center for a patient population of approximately 200,000 and the medical problems encountered are varied and challenging. It has the latest medical equipment and special care units including an 8 bed Pediatric ICU and a 28 bed Immediate Care ICU.

American Board Certification in Pediatrics and 2 years after residency required. Board Certification in subspecialty preferred.

Employment with ARAMCO will provide you with an interesting lifestyle in a multicultural environment, including comfortable family living arrangements, free medical care while in Saudi Arabia, fine schools and a broad spectrum of recreational opportunities, plus 36 days of vacation annually, allowing for extensive travel. We provide an attractive compensation package which includes an expatriate premium.

For immediate consideration, **CALL OUR 24 HOUR, 7 DAYS PER WEEK TOLL-FREE NUMBER 1-800-221-3333, EXT. R11,** or send resume to: **RES-R11, 7676 Hillmont, Suite 290, Dept. 06G-013-9, Houston, Texas 77040.**

ARAMCO

STREP TEST™
SHEEP BLOOD AGAR PLATES
LABORATORY CULTURE MATERIALS

- BACITRACIN DISKS
- URI-DIP®
  URINE CULTURE MATERIALS
- DELUXE INCUBATORS
- DISPENSERS
- INNOCULATING LOOPS
- SWABS

AVAILABLE FROM:
UNIVERSAL BIOLOGICAL LABS
DIAGNOSTIC DIVISION OF:
NATIONAL BIOLOGICAL CORPORATION

1532 ENTERPRISE PARKWAY
TWINSBURG, OHIO 44087
(216) 425-8180
OUTSIDE OHIO: 1-800-338-5045
IN OHIO: 1-800-227-6294

ORDER TODAY
FOR IMMEDIATE DELIVERY

HOUSE BASED PEDIATRICIANS (HBPs)

Huntington Memorial Hospital of Pasadena, California, a major affiliate of the University of Southern California School of Medicine, is seeking to hire four board eligible/certified pediatricians by July 1, 1989 to cover its 34-bed pediatric floor. These four house-based pediatricians (HBPs) will provide in-house coverage that traditionally would have been provided by pediatric interns or residents.

Founded in 1892, Huntington Memorial Hospital is a 606-bed non-profit medical center that serves the communities of the San Gabriel Valley of Los Angeles County. The total service area population of the San Gabriel Valley is approximately two million people. The Hospital offers a tertiary Infertility Center, Perinatal High-Risk Unit, a Neonatal ICU and renowned ECMO Center, a comprehensive Pediatric Center and a Pediatric ICU.

The compensation is competitive with the HMOs or other salaried positions in the area: $70,000 annual salary; health insurance (medical, dental, vision); life insurance ($50,000 term life); accidental death & dismemberment ($50,000); paid 3-week vacation; and a $1000 annual CME fund.

Those interested should send their CV and inquiries to Edgardo L. Arcinue, M.D., Head, Department of Pediatrics, 100 Congress Street, Pasadena, CA 91105; (818) 397-8688.

The Pediatric Forum

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

Advances in Neonatal Care

Sir.—Dr Goetzman's comments[1] on neonatal care draw a false and disturbing distinction. By suggesting that innovation is, or should be, divorced from research, he encourages the introduction of unproved technologies into the clinical arena. Unfortunately, history teaches us that premature, that is, unvalidated, use of technology in practice may have disastrous consequences. We need not look hard to find examples of how inadequate testing of medical interventions has adversely affected the lives of children: thalidomide, radiation treatment of "enlarged" lymphoid structures, and exchange transfusion for Reye's syndrome come to mind quickly.

Like Dr Goetzman, I applaud the willingness of our medical and nursing colleagues to explore new approaches to vexing problems. Unlike him, however, I am wary of the entrepreneurial drive to rush new ideas into practice without serious scrutiny. In fact, it is our moral duty to prevent unnecessary harm that might arise from the unintended consequences of innovation.

We can meet our obligation to minimize possible misadventure only by doing clinical research. The desire for a "quick fix" or rapid return on investment dollars does not justify a headlong plunge into very complicated and delicate waters.

JOEL FRADER, MD
Department of Pediatrics
Center for Medical Ethics
University of Pittsburgh
3705 Fifth Avenue at De Soto Street
Pittsburgh, Pa 15213-3417

1. Goetzman BW. Innovation and advances in neonatal care. *AJDC*. 1988;142:920.

In Reply.—I did not intend to "divorce" innovation from research in my commentary because it is often important in doing research. However, I did try to distinguish innovation and research as two different processes. Recognition of the innovative process, and that innovation is occurring in the clinical setting, is a logical first step in making it safer. Recognition of the hazards of clinical research has resulted in regulations that now make it safer and more ethical. Perhaps similar concepts will evolve regarding innovation.

Like Dr Frader, I am opposed to the "introduction of unproved technologies in the clinical arena" and would extend that to unproved nontechnologic interventions as well. While I remain a proponent of more and better clinical research, I would also like to remain open to advancement of medical care by other means.

BOYD W. GOETZMAN, MD, PHD
Division of Neonatology/TB 193
University of California
Davis, CA 95616

Incomplete Immunizations and the Computer

Sir.—I read the editorial "Incomplete Immunizations, Hospitalization, and Specialty Care"[1] with great interest. I agree with Tifft and Lederman[2] that incomplete immunizations are a major problem.

In the pediatrics ambulatory unit of the Catholic University of Rome, we employ a computerized immunization status calendar to record compulsory and noncompulsory immunizations. Documented, referred, and new immunizations are recorded, and parents are issued printed certificates of immunization status, along with a reminder of due dates.

This personal calendar facilitates both parent and physician compliance and awareness of immunization status. If regularly employed on a routine basis during hospitalization, it should help to minimize immunization deficiency, especially in the preschool-age child who tends to escape periodic control.

Furthermore, when immunizations are merely referred, and no documentation is available, we raise the question whether the cost involved in performing antibody assay to ascertain true immunization status may be more than justified.

VINCENZO CURRO, MD
Department of Pediatrics
Catholic University of Rome
Rome, 00168
Italy

1. Fulginiti VA. Incomplete immunizations, hospitalization, and specialty care. *AJDC*. 1988; 142:704.

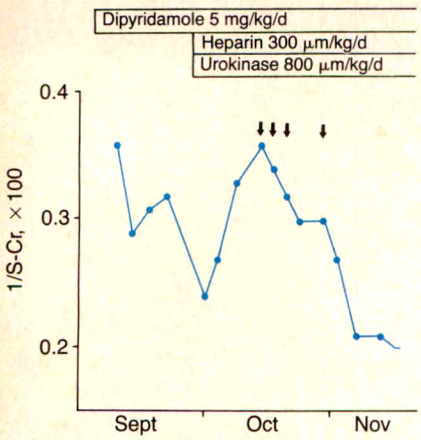
2. Tifft CJ, Lederman HM. Immunization status of hospitalized preschool-age children: the need for hospital-based immunization programs. *AJDC*. 1988;142:719-720.

Does Methylprednisolone Pulse Therapy Deteriorate the Course of Rapidly Progressive IgA Nephropathy?

Sir.—We read with interest the article by Welch et al[1] in the July 1988 issue of *AJDC*. They reported that methylprednisolone pulse therapy (MPT) given to three of five children who had rapidly progressive IgA nephropathy did not alter the course of disease in any of the patients. We report that MPT caused deteriorated renal function in a boy with IgA nephropathy. Careful consideration should be given to the use of MPT in children with IgA nephropathy.

Patient Report.—A 12-year-old boy, previously in good health and with no family history of renal disorders, was admitted to our hospital for investigation of microscopic hematuria, proteinuria, and deteriorated renal function. Urinary abnormalities had been detected at a school screening in 1986. At that time, his serum creatinine and blood urea nitrogen levels were within the normal range. Urinary abnormalities had been again detected in 1987, and he had remained asymptomatic. His local physician had measured his serum creatinine and blood urea nitrogen levels, which were 212 μmol/L and 14 mmol/L, respectively.

The boy's admission physical examination revealed no abnormalities, except anemic signs in the conjuctiva. His blood pressure was 128/88 mm Hg while receiving antihypertensive treatment. Laboratory data from renal function tests and serologic



Course of daily treatment administered to patient with IgA nephropathy. Dipyridamole was given from beginning, and heparin sodium and urokinase were added to daily treatment a half month after. Arrows indicate when methylprednisolone pulse therapy was administered. 1/S-Cr indicates reciprocal of serum creatinine.

tests performed were as follows: 24-hour creatinine clearance, 0.458 mL/s/1.73 m²; urinary protein level, 3.69 g/d; no aminoaciduria; blood urea nitrogen level, 17 mmol/L; serum creatinine level, 300 μmol/L; uric acid level, 0.48 mmol/L; sodium level, 137 mmol/L; potassium level, 5.5 mmol/L; total carbon dioxide level, 22.1 mmol/L; total protein level, 55 g/L; and albumin level, 28 g/L. The serum complement profile was normal. The antinuclear factor and hepatitis B surface antigen level were also negative. Urinalysis showed proteinuria (4+) and a large amount of occult blood. A percutaneous renal biopsy specimen showed almost globally sclerotic, mild mesangial proliferation, partially fibrous crescents with a predominant mesangial deposition of IgA and C3, and no vasculitis. Rapidly progressive IgA nephropathy was diagnosed, and MPT (500 mg/d) was given intravenously over a one-hour period three times every other day. This was repeated one week later. Following MPT, we found, with time, a sudden decline in the slope of the reciprocal of serum creatinine and stopped further treatment (Figure).

Comment.—Our patient had a few features in common with the patients described by Welch et al[1]: a boy with mesangial deposition of IgA and C3, hypertension, and nephrotic-range proteinuria. We agree with Welch et al that we should be careful in our treatment of a child with the clinical features mentioned above.

Rapidly progressive glomerulonephritis (RPGN) has several causative bases and refers to the clinical syndrome of rapid and progressive decline in renal function, which, without treatment, will usually result in end-stage renal failure in a matter of weeks or months.[2] When considering the treatment of patients with RPGN, one should know that only positive responses to MPT have been reported, and MPT is thought to be the most effective therapy, although it has not yet been shown in a controlled study[3] to be beneficial. We think there is a possibility that patients whose renal function was deteriorated by MPT have been mistakenly believed to be nonresponders to MPT.

Cole et al[4] suggested that MPT may be beneficial in treating some children with severe "proliferative" glomerulonephritis. Our patient's renal biopsy specimen showed globally sclerotic lesions with mild mesangial proliferation. The likelihood of a patient's positive response to therapy for RPGN is thought to be primarily related to the severity of the disease at the time treatment is initiated. Our patient had had hematuria and proteinuria for 1½ years before coming to us. Had he undergone a biopsy at that time, a typical IgA nephropathy with more mesangial proliferation might have been found, and a positive response to MPT might have occurred. However, MPT had no effect on the disease process in the cases of Welch et al and worsened our patient's condition. The mechanism of action of MPT in our case is unknown. We need to study further the effectiveness of MPT in children with IgA nephropathy and to determine the factors that will allow the disease process to no longer be altered or worsened by MPT.

Noritomo Itami, MD
Yasushi Akutsu, MD
Yukihiro Kusunoki, MD
Hiroyuki Tochimaru, MD
Yasuo Takekoshi, MD
Hokkaido University School of Medicine
Department of Pediatrics
North 15 West 7, Kitaku
Sapporo, 060 Japan

The authors are grateful to Prof Shuzo Matsumoto, MD, for helpful advice.

1. Welch TR, McAdams J, Berry A: Rapidly progressive IgA nephropathy. *AJDC* 1988;142:789-793.

2. Rose BD, Jacobs JB: Nephrotic syndrome and glomerulonephritis, in Rose BD (ed): *Pathophysiology of Renal Disease*, ed 2. New York, McGraw-Hill International Book Co, 1987, pp 179-296.

3. Couser WG: Rapidly progressive glomerulonephritis: Classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis* 1988;11:449-464.

4. Cole BR, Brocklebank JT, Kienstra RA, et al: 'Pulse' methylprednisolone therapy in the treatment of severe glomerulonephritis. *J Pediatr* 1976;88:307-314.

In Reply.—The case reported by Itami et al is consistent with our belief that MPT does not improve the course of rapidly progressive IgA nephropathy. As we stated in our article, such therapy was attempted in three of the five patients with no discernible benefit. The rationale for using the therapy in these patients had been our apparent success in using MPT for the treatment of some patients with idiopathic RPGN.[1] In retrospect, it is obvious to us that this approach is of no use in rapidly progressive IgA nephropathy or in any other crescentic immune complex glomerulonephritis. Whether such therapy can actually hasten the deterioration in renal function is not clear. With a creatinine clearance of 27.5 mL/min/1.73 m² and a biopsy specimen showing globally sclerotic glomeruli, it would seem that the renal function of the patient of Itami et al was destined to deteriorate whether or not any therapy was undertaken.

Whether corticosteroids have a place in the therapy for patients with more typical IgA nephropathy is also unknown. We are currently conducting a double-blind placebo-controlled cross-over study to address this issue. In the meantime, we do not believe that there is any firm evidence to support the use of any type of corticosteroid therapy in either form of IgA nephropathy.

Thomas R. Welch, MD
A. James McAdams, MD
Annette Berry
Departments of Pediatrics and Pathology
Divisions of Nephrology and Pathology
University of Cincinnati School of Medicine
Children's Hospital Research Foundation
Elland and Bethesda avenues
Cincinnati, OH 45229-2899

1. Davis CA, McEnery PT, Maby S, et al: Observations on the evolution of idiopathic rapidly progressive glomerulonephritis. *Clin Nephrol* 1978;9:91-101.

Parent-Child Minimal Change Nephrotic Syndrome

Sir:—Choi et al[1] reported the occurrence of nephrotic syndrome in a father and daughter. The parent and child developed the nephrotic syn-

drome at 22 and 8 years of age, respectively. The father had biopsy-proved minimal change nephrotic syndrome and his daughter was presumed to have the same lesion, based on her clinical presentation and response to prednisone therapy. Choi et al also cited a report by White[2] of another father and daughter with steroid-responsive nephrotic syndrome.

We are aware of another occurrence of minimal change nephrotic syndrome in a parent and child. In 1979, Schwartz and Cornfeld[3] reported a case of a mother and son who had relapsing steroid-responsive nephrotic syndrome. The mother's brother also developed the nephrotic syndrome. The mother and brother developed the nephrotic syndrome at ages 8 and 12 years, respectively. They both had a renal biopsy specimen demonstrating minimal glomerular changes. The son developed the nephrotic syndrome at 3 years of age. Based on his clinical presentation and prompt response to prednisone therapy, he probably also had minimal change nephrotic syndrome.

We agree with Choi et al that while familial forms of minimal change nephrotic syndrome usually involve only siblings, parent-child occurrences of this disease have been found, although they are very uncommon.

ALEXANDER K. C. LEUNG, MBBS, FRCPC
WILLIAM LANE M. ROBSON, MD, FRCPC
Department of Pediatrics
University of Calgary
Alberta Children's Hospital
Calgary, Alberta
Canada T2T 5C7

1. Choi Y, Paul JV, Ferguson CL: Parent-child minimal change nephrotic syndrome. *AJDC* 1988; 142:1140.
2. White RHR: The familial nephrotic syndrome: I. A European survey. *Clin Nephrol* 1973; 1:215-219.
3. Schwartz W, Cornfeld D: An unusual variation of familial nephrosis. *AJDC* 1979;133:216-217.

Gonococcal Conjunctivitis Mimicking Orbital Cellulitis in a Young Adolescent

Sir.—Infection by *Neisseria gonorrhoeae* is the most common reportable disease in the United States.[1] Conjunctivitis, however, is a rare manifestation of gonococcal infection beyond the neonatal period.[2,3] An outbreak of gonococcal conjunctivitis (GCC), which included some children, has been reported during an epidemic of acute hemorrhagic conjunctivitis, when urine-containing eye drops were used as a folk remedy.[4,5] There are few reports of sexually transmitted GCC in adolescents.[6] We describe a young adolescent female with GCC who was initially thought to have orbital cellulitis.

Patient Report.—A previously healthy 13-year-old girl developed redness, mild swelling, and discharge from her left eye 2 days before admission. A physician who examined her diagnosed conjunctivitis and prescribed antibiotic eye drops. The eye discharge increased and she developed a burning sensation of the eye, photophobia, and frontal headache. She felt warm, anorexic, fatigued, and nauseated with mild, crampy midabdominal pains. The symptoms worsened, and she discontinued the eye drops and came to the emergency department at Saint Christopher's Hospital for Children, Philadelphia, Pa. There were no associated upper respiratory tract symptoms, sore throat, recent eye trauma, dysuria, or vaginal discharge, and she denied sexual activity.

She was uncomfortable and had a temperature of 37.5°C. Her left palpebral and bulbar conjunctivae were severely hyperemic, with chemosis and copious drainage of a thick yellowish green nonbloody discharge. There was moderate, nontender, periorbital swelling, and no proptosis. The cornea was slightly clouded and the retina was normal. Ocular motility was limited and painful. There were three 1-cm tender left preauricular lymph nodes. The remainder of the physical examination results were normal.

A Gram stain of the eye discharge showed many neutrophils and intracellular and extracellular gram-negative diplococci. Specimens for culture were obtained. She was admitted with a diagnosis of orbital cellulitis, received ceftriaxone intravenously, erythromycin ophthalmic ointment, and 2% cyclopentolate hydrochloride (a mydriatic). A computed tomographic scan showed no orbital involvement. *Neisseria gonorrhoeae* (β-lactamase negative) was subsequently isolated from eye and throat specimens. Cervical and rectal cultures for *N gonorrhoeae* and cervical swab for chlamydia fluorescent antibody were negative.

Her condition improved in 48 hours, and a 5-day course of intravenous ceftriaxone was completed. Her infection resolved without sequelae.

Comment.—Gonococcal conjunctivitis must be considered in adolescents with purulent conjunctivitis.[6] Without appropriate cultures, the diagnosis of this treatable infection, which has potential for permanent visual damage,[3] will be delayed.

The transmission of *N gonorrhoeae* in this patient probably involved sexually acquired gonococcal pharyngitis and autoinoculation of the conjunctivae. The majority of reports of GCC in adults are associated with symptomatic genital infection.[2,3,6] Our patient's diagnosis demonstrates that asymptomatic gonococcal infection may be a source of GCC.[7]

Gonococcal conjunctivitis with prolonged incubations has been reported,[8,9] but in most instances an acute onset associated with hyperpurulent discharge, severe conjunctival inflammation, and tender periocular edema is noted. Gonococcal conjunctivitis can mimic orbital cellulitis with pain, gaze restriction, and chemosis.

The diagnosis of GCC should be supported by Gram's stain and confirmed by culture of all appropriate sites[3,5,6] (pharynx, genitalia, and rectum). The coexistence of other sexually transmitted diseases must also be considered.

The Centers for Disease Control, Atlanta, Ga, recommends that all patients with GCC be hospitalized for 5 days of intravenous penicillin or third-generation cephalosporin therapy.[10] Local therapy with saline lavage and topical antibiotic ointment is also indicated.[11] Most patients with GCC treated in this manner have a rapid response. Ophthalmologic follow-up and culture for test of cure are mandatory.

AGUSTIN LEGIDO, MD
MARK JOFFE, MD
Department of Emergency Medicine
Saint Christopher's Hospital for Children
Fifth and Lehigh avenues
Philadelphia, PA 19133

1. Centers for Disease Control. Table 1. Summary-cases of specified notifiable diseases, United States. *MMWR*. 1986;34:782.
2. Korting HC, Neubert V, Abeck D, Jordan R, Luderschmidt C. Gonoblennorrhea adultorum (gonococcal conjunctivitis): a 'disappearing disease' which does not disappear. *Dermatologica*. 1985;170:17-21.
3. Wan WL, Farkas GC, May WN, Robin JB. The clinical characteristics and course of adult gonococcal conjunctivitis. *Am J Ophthalmol*. 1986;102:575-583.
4. Valenton M. Abendanio R. Gonorrheal conjunctivitis. *Can J Ophthalmol*. 1973;8:421-427.
5. Alfonso E, Friedland B, Hupp S, et al. *Neisseria gonorrhoeae* conjunctivitis. *JAMA*. 1983;250:794-795.
6. Buchta RM. Hemorrhagic *Neisseria gonorrhoeae* conjunctivitis in an adolescent female. *Adolesc Health Care*. 1986;7:60-61.
7. Frazier JJ, Miller J, Pickering LK. Orbital cellulitis due to *Neisseria gonorrhoeae* in an enucleated socket. *Arch Ophthalmol*. 1979;97: 2345.

8. Podgore JK, Holmes KK. Ocular gonococcal infection with minimal or no inflammatory response. *JAMA*. 1981;246:242-243.
9. Bruins SC, Tight RR. Laboratory-acquired gonococcal conjunctivitis. *JAMA*. 1979;241:247.
10. Centers for Disease Control. 1985 STD Treatment Guidelines. *MMWR*. 1985;34:75S.
11. Ullman S, Roussel TJ, Forster RK. Gonococcal keratoconjunctivitis. *Surv Ophthalmol*. 1987;32:199-208.

Polymicrobial Bacteremia and Child Abuse

Sir.—We read with interest Bonadio's recent article[1] about polymicrobial bacteremia in children. The author presents an extensive list of underlying conditions associated with this unusual condition. We wish to add child abuse as another important cause of polymicrobial bacteremia.

Adult-induced sepsis in children has been described in several reports[2-6] as a manifestation of Munchausen syndrome by proxy. This syndrome described by Meadow[2] is a variant of child abuse in which parents, usually mothers, fabricate signs and symptoms of illness in their children. In some cases, fabrication is done by deliberate injection of bacteriologically contaminated material. The special features that should suggest exogenously induced bacteremia are the following: (1) recovery of unusual organisms that are not commonly pathogens, (2) development of frequent skin infections at the site of intravenous infusions, (3) absence of an underlying condition or source of infection that would explain the development of polymicrobial bacteremia, and (4) recurrent polymicrobial bacteremia. The presence of an indwelling intravenous catheter does not exclude induced infection; indeed, most of the reported cases of induced bacteremia occurred in patients with intravenous lines.

The mothers of these patients almost always appear to be "caring and attentive." They frequently are nurses or have been trained in nursing techniques. They spent long hours at the bedside and are "very involved" in the care of their child. The underlying psychopathology remains poorly understood and even after psychiatric evaluation, a specific diagnosis usually cannot be made. Although the motives for this bizarre behavior are not known, the consequences may be severe. In one review of Munchausen by proxy,[7] 3 of 11 children died. Thus, we urge consideration of this diagnosis in cases of polymicrobial bacteremia with the features outlined above.

JACOB AMIR, MD
Department of Pediatrics
St Louis Children's Hospital
400 S Kingshighway Blvd
St Louis, MO 63110

1. Bonadio WA. Polymicrobial bacteremia in children: an 11-year experience. *AJDC*. 1988; 142:1158-1160.
2. Meadow SR. Munchausen syndrome by proxy: the hinterland of child abuse. *Lancet*. 1977; 2:343-345.
3. Kohl S, Pickering LK, Dupree E. Child abuse presenting as immunodeficiency disease. *J Pediatr* 1978;93:466-468.
4. Liston TE, Levine PL, Anderson C. Polymicrobial bacteremia due to Polle syndrome: the child abuse variant of Munchausen by proxy. *Pediatrics*. 1983;72:211-213.
5. Halsey NA, Frentz JM, Tucker TW, Sproles T, Redding J, Daum RS. Recurrent nosocomial polymicrobial sepsis secondary to child abuse. *Lancet*. 1983;2:558-560.
6. Rubin LG, Agelides A, Davidson M, et al. Recurrent sepsis and gastrointestinal ulceration due to child abuse. *Arch Dis Child*. 1986;61:903-905.
7. Shnaps V, Frand M, Rotem Y, Tirosh M. The chemically abused child. *Pediatrics* 1981;68: 119-121.

Risks of Placing One-Way Valves in Ventilator Circuits

Sir.—The article by Outwater et al[1] in the May 1988 issue of *AJDC* was noted with great interest. This excellent report outlines the methods and techniques developed at Boston's Floating Hospital for delivering ribavirin (Virazole) during ventilation with the Healthdyne 102 ventilator (Healthdyne Inc, Marietta, Ga). Demers et al[2] described alternative circuitry for use with pressure- and volume-preset ventilators.

Several differences between the circuitry employed by Outwater et al and the systems described by Demers and coworkers can be observed. Of particular significance is the presence of a one-way valve interposed between the ventilator and the junction of the ventilator's inspiratory tubing, and the outflow tube of the small-particle aerosol generator (SPAG) (Viratek, ICN Pharmaceuticals, Costa Mesa, Calif) in the configuration developed by Outwater and colleagues.

The purpose of the one-way valve at that position is to prevent retrograde flow from the small-particle aerosol generator to the ventilator. To the extent that such retrograde flow actually occurs, there would be a tendency for crystalline drug to provoke ventilator malfunction. In fact, however, such retrograde flow should never occur. In the absence of retrograde flow, of course, the one-way valve becomes superfluous and is strictly not indicated.

Furthermore, we must recognize that the placement of a one-way valve in that position is decidedly contraindicated with certain ventilator models. With several brands (eg, the Bourns BP-200, the Bourns Bear Cub [Bear Medical Systems Inc, Riverside, Calif] and the Sechrist IV-100B [Sechrist Industries Inc, Anaheim, Calif]) the interposition of a one-way valve anywhere in the inspiratory limb isolates the patient from the pressure relief ("pop-off") mechanism incorporated within the inspiratory circuit of the ventilator. This will, in turn, frustrate the alarm/dumping function of the pop-off mechanism and can expose the patient to dangerously high peak pressures and attendant barotraumatic sequelae.

Therefore, clinicians who might wish to place a one-way valve in the ventilator's inspiratory limb should make sure that it will not interfere with the pressure relief mechanism. One way of determining this at the bedside with a given ventilator is to occlude both the patient connection port and the exhalation valve with the one-way valve in place and observe the machine's response. If the ventilator fails to dump appropriately, the one-way valve's presence is contraindicated and it should be removed before connecting the patient to the system.

Clinicians who want to safeguard against any possible retrograde flow of drug into the ventilator's heated humidifier may do so by interposing a breathing circuit filter (Pall BB-50T) between the humidifier and the SPAG T-piece. This will serve their purpose without interfering with the ventilator's overpressure features.

BOB DEMERS, RRT
Demers Consulting Services
PO Box 2326
Stanford, CA 94309
RONALD W. MIKE, RRT
Respiratory Care Department
University of Massachusetts
Medical Center
55 Lake Ave N
Worcester, MA 01655

1. Outwater KM, Meissner HC, Peterson MB: Ribavirin administration to infants receiving mechanical ventilation. *AJDC* 1988;142:512-515.
2. Demers RR, Parker J, Frankel LR, et al: Administration of ribavirin to neonatal and pediatric patients during mechanical ventilation. *Respir Care* 1986;31:1188-1196.

For the symptoms of allergic rhinitis...

DESIGNED TO DELIVER

Now NASALCROM® is available in the ready-to-use pump spray your patients have been asking for! The new NASALMATIC® fully-assembled unit comes in two convenient sizes: For your chronic allergic rhinitis patients, the *new* 26 mL size is a handy, economical alternative to the purchase of frequent refills. For your patients with seasonal symptoms, the regular 13 mL size is ideal.

Inside the new NASALCROM unit is the proven formula patients rely on for relief of sneezing, itching, runny nose, and congestion.[1,2] NASALCROM provides protection from the first dose[1] and symptom relief within days.[2] And it works without the annoying side effects typical of other first-line allergic rhinitis medications.[3,4]

Nonsedating NASAL SOLUTION, 40 mg/mL

NASALCROM®

(cromolyn sodium/FISONS)

IN THE NEW FULLY-ASSEMBLED UNITS (26 mL AND 13 mL)

Please see adjacent page for Brief Summary of Full Prescribing Information.

NASAL SOLUTION, 40 mg/mL

NASALCROM®

(cromolyn sodium nasal solution, USP)

Brief Summary

DESCRIPTION: Each milliliter of NASALCROM® Nasal Solution (cromolyn sodium nasal solution, USP) contains 40 mg cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA (edetate disodium) to stabilize the solution.

INDICATIONS: NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.

CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.

PRECAUTIONS: General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy.

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphylaxis.

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

CAUTION: Federal law prohibits dispensing without prescription.

References:

1. Pelikan Z, Pelikan-Filipek M: The effects of disodium cromoglycate and beclomethasone dipropionate on the immediate response of the nasal mucosa to allergen challenge. *Ann Allergy* 1982;49:283-292.
2. Data on file, Fisons Corporation. From perennial allergic rhinitis trial by Wittig HJ, with Cohan RM, Bloom FL, Rhoades RB, et al.
3. *Physicians' Desk Reference® (PDR®),* ed 42. Oradell, NJ, Medical Economics Co Inc, 1988. Beconase® (beclomethasone dipropionate, USP), pp 1004-1005; Seldane® (terfenadine), pp 1426-1427.
4. *Physicians' Desk Reference for Nonprescription Drugs® (PDR®),* ed 9. Oradell, NJ, Medical Economics Co Inc, 1988. Afrin® (oxymetazoline hydrochloride), p 685; Chlor-Trimeton® (chlorpheniramine maleate), pp 686-687; Actifed® (pseudoephedrine hydrochloride, triprolidine hydrochloride), p 530; Sudafed® (pseudoephedrine hydrochloride), pp 533-534.

FISONS

Pharmaceuticals
Prescription Products
Rochester, NY 14623

© 1989 Fisons Corporation

FIS-048

Death Investigation—United States, 1987

In the United States, medical examiners and coroners (ME/Cs) are responsible for investigating violent, suspicious, or unexpected deaths and deaths that are unattended by a physician.

In 1981, the Office of Maternal and Child Health compiled information on the death investigation systems in the United States.[1] To update this information, during fall 1987, CDC surveyed either the state ME's office, the state vital registrar's office, or the state ME/C's association. Current information was obtained for all states except Alaska, Arizona, Colorado, Iowa, Nevada, and Ohio. For these six states, information is from the 1981 report.

There are three basic types of death investigation systems:

1. Medical Examiner. Nineteen states and the District of Columbia have a state chief ME who is responsible for investigating deaths for the entire state.

2. Coroner. Twelve states have county or district coroners who are responsible for investigating deaths within each county.

3. Mixed Medical Examiner and Coroner. Thirteen states have county or district death investigation systems, some of which are directed by MEs and some by coroners. In these states, no one person has supervisory responsibility for the state. However, three states—Arkansas, Kentucky, and Montana—have an appointed state chief ME and elected county coroners.

Information gathered in this survey has identified states that have centralized supervision of death investigations and, therefore, greater uniformity in investigation procedures and data. This information should allow each state to compare its system with that of other states and to facilitate the exchange of ideas on improving death investigation systems.

Reference

1. Health Services Administration. Death investigation: synopsis and analysis of laws (including sudden infant death syndrome (SIDS) legislation) in 56 US jurisdictions (1980). Washington, DC: US Department of Health and Human Services, Public Health Service, 1981. Final report, contract no. HSA-240-80-0027.

Education about Adult Domestic Violence in U.S. and Canadian Medical Schools, 1987-88

APPROXIMATELY 4 million spouses are beaten annually in the United States,[1] and the rate of violence among college student dating partners on some campuses may approach that found within marriage.[2,3] Despite substantial estimates of the magnitude of adult domestic violence (ADV), evidence exists that physicians and other health-care workers require further instruction in recognizing and treating these problems.

The Surgeon General's Workshop on Violence and Public Health[4] and the Attorney General's Task Force on Family Violence[5] recommend that curricula of medical schools and other relevant professional schools include education about domestic violence. To determine current curriculum content about ADV, all 147 accredited U.S. and Canadian medical schools were surveyed during the 1987-88 academic year by the New Jersey Medical School Domestic Violence Prevention Project (NJMS DVPP).

Representatives of 116 schools (81%) responded to the survey. Of those 116 schools, 61 (53%) indicated that their students did not receive any instruction about ADV; 49 (42%) reported that their students received such instruction as part of at least one required course; and six (5%) reported that their students received no required instruction about ADV but could choose to receive such instruction as part of an elective.

Overall, 77 courses that included at least one session of instruction about ADV were identified.

Of all sessions addressing ADV, 68% were offered in the first 2 years of medical school. Departments of psychiatry or other behavioral sciences taught 63% of all sessions on ADV; family practice, 7%; geriatrics, 7%; and internal medicine, 7%.

Reported by: HA Holtz, MD, C Hanes, MPH, New Jersey Medical School, Univ of Medicine and Dentistry of New Jersey. MA Safran, College of Medicine, State Univ of New York Health Science Center, Syracuse. Intentional Injuries Section, Epidemiology Br, Div of Injury Epidemiology and Control, Center for Environmental Health and Injury Control, CDC (MMWR vol 38, No. 2).

CDC Editorial Note: Within the past decade, ADV has been identified as a major public health problem in the United States.[4,6,7] No surveillance of ADV exists, and assessment of the magnitude and impact of this problem is difficult. To help physicians better detect and properly refer victims and potential victims of domestic violence, the American College of Obstetricians and Gynecologists (ACOG) recently sent information about battered women to its 28,000 members.[8,9]* This material suggests that women identified as domestic abuse victims should be provided information about women's rights, available community resources, and strategies to deal with abusive relationships.

This survey may be the first attempt to determine the prevalence of school instruction about ADV. The finding

that 58% of the responding schools do not require instruction about ADV may be conservative because schools were classified as offering such instruction even if such training was limited to one category of abuse, such as elder abuse or spouse abuse. No attempt was made to determine whether schools that offer ADV instruction were more likely to respond to the survey, nor was any attempt made to evaluate the prevalence of instruction that may not be specified in the curriculum (e.g., direct clinical contact with abuse victims).

An increase in demand for protective and rehabilitative services occurred when reporting of child abuse became more common after the widespread adoption of mandatory reporting laws in the 1960s.[10] Similarly, curricular changes that increase detection and referral rates for ADV might further increase demand for community services. Medical education and community efforts in both child abuse and ADV should promote not only effective recognition, treatment, and referral of victims but also primary prevention. As a first step, a suggested hospital protocol[11] and a curriculum description and training manual for health educators[12] will be distributed by the NJMS DVPP to the surveyed faculty members requesting them. Further examination of medical school curricula about ADV and evaluation of methods of such seeded. The methods that best promote effective treatment and prevention should then be disseminated to all programs and/or facilities that train health professionals.

Additional information may be obtained from the NJMS DVPP, University Hospital, I-246150 Bergen St., Newark, NJ 07103-2757; or from the Jersey Battered Women's Service, Inc., (201) 455-1256.

References

1. Straus MA, Gelles RJ, Steinmetz SK. Behind closed doors: violence in the American family. Garden City, New York: Anchor Press/Doubleday, 1980.
2. Makepeace JM. Life events stress and courtship violence. Fam Relations 1983;32:101-9.
3. Cate RM, Henton JM, Koval J, Christopher FS, Lloyd S. Premarital abuse: a social psychological perspective. J Fam Issues 1982;3:79-89.
4. US Department of Health and Human Services, US Department of Justice. Surgeon General's Workshop on Violence and Public Health: report. Washington, DC: US Department of Health and Human Services, Public Health Service, 1986.
5. US Department of Justice. Attorney General's Task Force on Family Violence: final report. Washington, DC: US Department of Justice, 1984.
6. Rosenberg MI, Stark B, Zahn MA. Interpersonal violence: homicide and spouse abuse. In: Last JM, ed. Public health and preventive medicine. 12th ed. Norwalk Connecticut: Appleton-Century-Crofts, 1986.
7. Stark E, Flitcraft A, Zuckerman D, Grey A, Robison J, Frazier W. Wife abuse in the medical setting: an introduction for health personnel. Rockville, Maryland: National Clearinghouse on Domestic Violence, 1981. (Domestic violence monograph series no. 7).
8. American College of Obstetricians and Gynecologists. The battered woman. Washington, DC. American College of Obstetricians and Gynecologists, 1989. (ACOG technical bulletin no. 124).
9. American College of Obstetricians and Gynecologists. The abused woman. Washington, DC: American College of Obstetricians and Gynecologists, 1988. (ACOG patient education pamphlet no. AT083).
10. Newberger EH. The helping hand strikes again: unintended consequences of child abuse reporting. In: Newberger EH, Bourne R, eds. Unhappy families: clinical and research perspectives on family violence. Littleton, Massachusetts: PSG Publishing, 1985;171-8.
11. Braham R, Furniss K, Holtz H, Stevens ME. Hospital protocol on domestic violence. Morristown, New Jersey: Jersey Battered Women's Service, Inc, 1986.
12. Braham R, Furniss K, Holtz H. Hospital training on domestic violence. Morristown, New Jersey: Jersey Battered Women's Service, Inc, 1986.

*For more information, contact: ACOG, Resource Center, 409 12th St., SW, Washington, D.C., 20024-2188.

Editorial Freedom and Integrity

Statement of the International Committee of Medical Journal Editors:

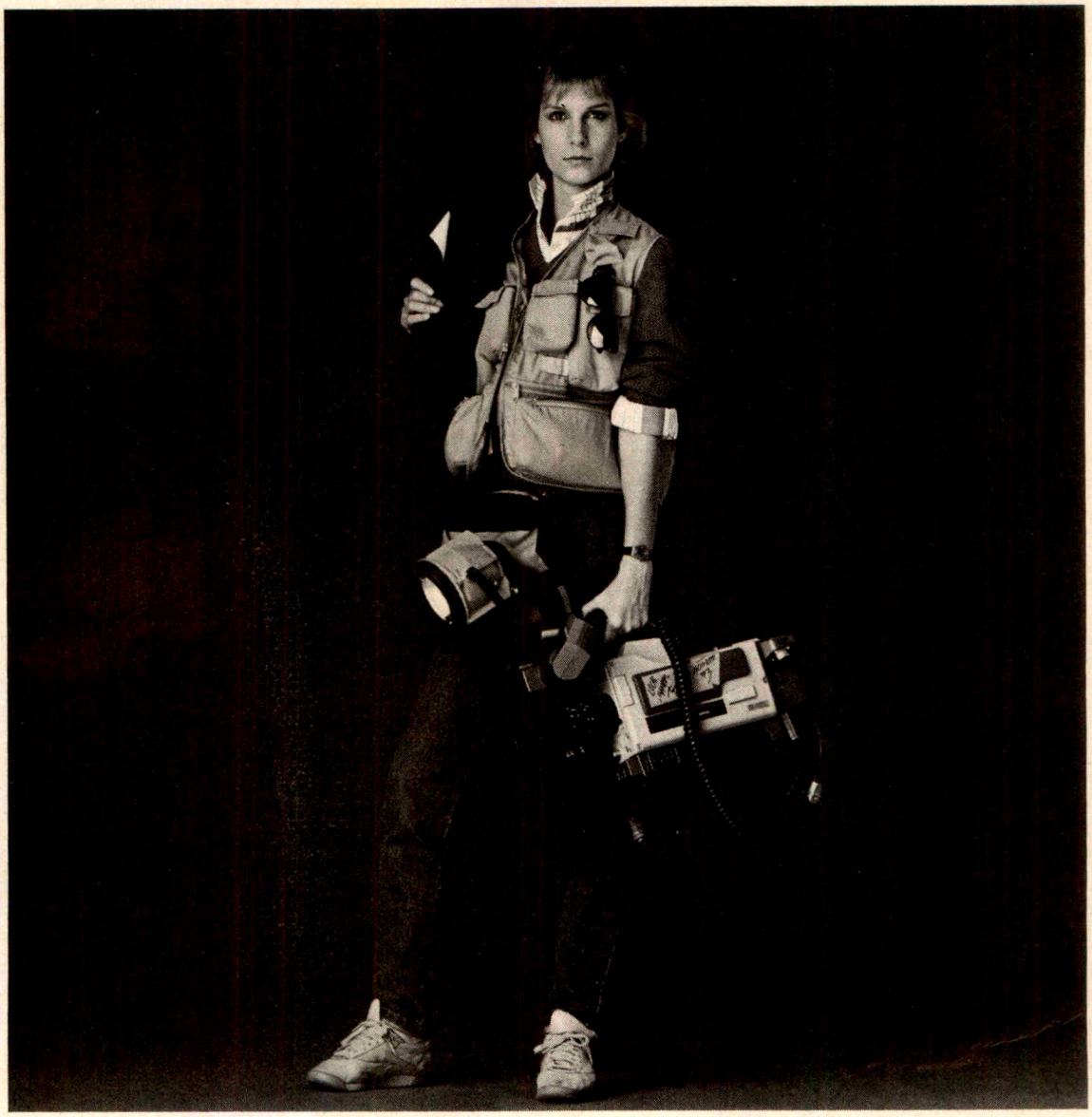
Medical journal owners and editors have a common endeavor, the publishing of a reliable and readable journal, published with due respect for the stated aims of the journal and for costs. The function of owners and editors, however, are different. The owners have the right to appoint and dismiss editors and to make important business decisions, in which editors should be involved to the fullest extent possible. Editors must have full authority for determining the editorial content of the journal. This concept of editorial freedom should be resolutely defended by editors even to the extent of placing their positions at stake. To secure this freedom in practice, the editor should have direct access to the highest level of ownership, not only to a delegated manager.

Medical journal editors should have a contract that clearly states the editor's rights and duties in addition to the general terms of the appointment and defines mechanisms for resolving conflict.

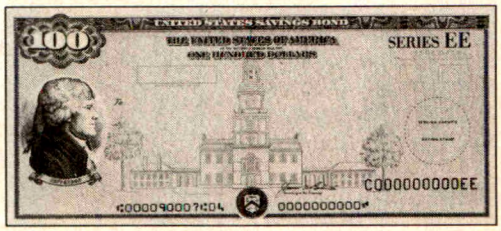
An independent editorial advisory board may be useful in helping the editor establish and maintain editorial policy.

All editors and editor's organizations have the obligation to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical community.

Portrait of the Great American Investor



She's never in one place for long. Wherever the story takes her, she'll go. She invests her time in her work and her money in U.S. Savings Bonds.



Over 23 million Americans like her invest in Savings Bonds. They are the Great American Investors. People everywhere are discovering that Bonds have changed. When held five years or more, Bonds pay competitive rates, like money market accounts. And they're free from state and local income tax.

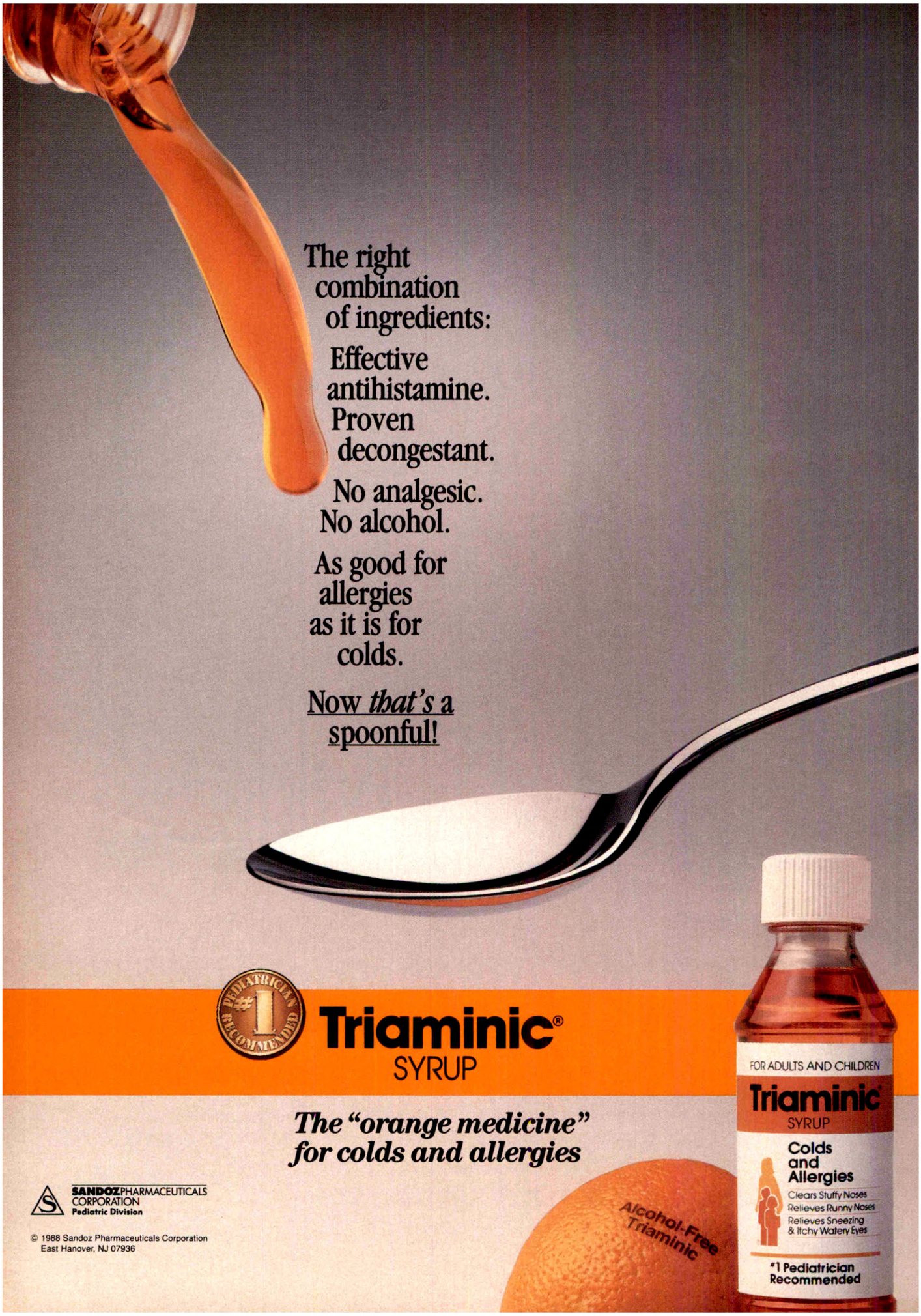
Bonds are easy to buy. You can purchase them at most banks or though Payroll Savings at work. So, whether you are investing $25 or $5000, buy U.S. Savings Bonds. The Great American Investment.

Find out more, call 1-800-US-BONDS.

U.S. SAVINGS BONDS
THE GREAT AMERICAN INVESTMENT

Bonds held less than five years earn a lower rate.

A public service of this publication.


The right combination of ingredients:
Effective antihistamine.
Proven decongestant.
No analgesic.
No alcohol.
As good for allergies as it is for colds.
Now *that's* a spoonful!
#1 PEDIATRICIAN RECOMMENDED
Triaminic®
SYRUP
The "orange medicine" for colds and allergies
SANDOZ PHARMACEUTICALS CORPORATION
Pediatric Division
© 1988 Sandoz Pharmaceuticals Corporation
East Hanover, NJ 07936
Alcohol-Free Triaminic
FOR ADULTS AND CHILDREN
Triaminic
SYRUP
Colds and Allergies
Clears Stuffy Noses
Relieves Runny Noses
Relieves Sneezing & Itchy Watery Eyes
#1 Pediatrician Recommended

Neonatal Intensive Care

At What Price?

The March 24/31, 1989, issue of *The Journal of the American Medical Association* is dedicated to timely and important topics relating to newborn medicine. These include articles dealing with perinatal infections[1-3] and prenatal dilemmas.[4,5] The contents of this issue of *JAMA* are important and relevant to health care professionals who render care to pregnant women and their children.

Three articles in particular are of great significance to pediatricians caring for infants who may have spent many weeks or months in a modern neonatal intensive care unit. Allen et al[6] comment on demographic characteristics associated with neonatal intensive care after-discharge mortality in Georgia. They found that infants who died after discharge had a median duration of neonatal intensive care unit hospitalization of 20 days (only twice as long as the "average" length of stay in most neonatal intensive care units) and a median birthweight of 1983 g. These infants succumbed to congenital heart disease, sudden infant death syndrome, and infection. It is striking to note that the infants described in their study were not the smallest and sickest infants we usually associate with the highest mortality rate after discharge.

In view of the large number of infants dying of congenital heart disease, and despite newer developing modalities for treating certain forms of heart disease once felt to have a hopeless prognosis (hypoplastic left-heart syndrome), we must strive for ongoing improvement in surgical and medical treatment of congenital heart disease. Nearly one quarter of the infant deaths in the study conducted by Allen et al[6] were caused by sudden infant death syndrome. Although certain risk factors for this disorder can be clearly identified (maternal tobacco use, prematurity of birth), our methods for "monitoring" and treating the infant at risk are far from ideal. Despite widespread and liberal use of home cardiorespiratory monitors, infants still die of this disorder. The efficacy of monitoring has yet to be proved. Perhaps Nelson[7] was correct in wondering "But who shall monitor the monitor?"

The editorial by Stahlman[8] and the report by McCormick[9] should strike a very familiar chord in physicians and nurses working in neonatal intensive care units, and in the physicians and families caring for these infants after discharge.

Despite a review of 20 years' experience with neonatal intensive care suggesting that more infants survive free of moderate to severe handicap, McCormick questions whether such findings based on early outcome analysis are sufficient to characterize later outcomes, particularly those identified as these children enter school. McCormick notes that we must have ongoing concerns about long-term outcomes. Further definition of these outcomes is crucial to assess the utility of interventions, both in the neonatal intensive care unit and after discharge.

Stahlman,[8] a pioneer in neonatology who has greatly advanced our knowledge of lung physiology and development, raises some very important ethical and moral concerns regarding the role of technology and research in neonatal intensive care. She points out that basic advances in neonatology 20 years ago became possible because of important advances in miniaturization of treatment modalities. Clearly, the development of tools taken for granted now (small-bore endotracheal tubes and plastic umbilical catheters) revolutionized the care of low-birth-weight infants. (Present pediatric residents could not possibly imagine neonatal care without these "basics"!) Dr Stahlman succinctly notes that as technology became increasingly complex, specialized personnel were needed (eg, respiratory therapists), and as a consequence, increasing numbers of very-low-birthweight infants can survive and be discharged from modern neonatal intensive care units. With the latest technologic developments permitting much of the care we render, neonatal medicine has become engulfed in caring for tiny, tiny infants. We must question ourselves and ask whether we are nearing the limits of the care we can provide for infants born at 24 weeks' gestation. The question has been asked before, and we must ask it again: How small is too small?[10]

Stahlman[8] notes that initial costs of neonatal intensive care for tiny infants (up to several hundred thousand dollars) becomes magnified and multiplied many times over when we realistically look at a lifetime of handicap and ongoing and demanding specialized medical care. There is no doubt that innumerable infants have been saved, leading to happy and grateful parents and grandparents. However, we must not forget our less fortunate patients. Stahlman accurately states that "with successes have come failures, on an equally grand scale." I am not sure parents thank us for saving an infant who develops severe, profound mental retardation, and is deaf and blind. Sometime during the day-to-day performance of our duties, someone will raise questions about the quality of life.

Technology and research have been driving forces in neonatal intensive care. We must ask ourselves over and over, "At what price?" I ask myself this question every time I drive home at 3 AM after stabilizing a critically ill 550-g, 24- to 25-week gestation infant and can sum it up no better than Lucey,[11] who elegantly states:

> The prematurely born infant emerges into a hectic, cold, noisy, and bright environment filled with mysterious equipment and masked strangers who try to help. Almost everything done to or for the infant is painful and that pain can certainly be felt . . . The

infant who must have an endotracheal tube cannot cry and may not be fed by mouth for weeks. His or her feet are slashed periodically for blood samples. The infant's respirator whirrs away night and day keeping his or her lungs inflated and sustaining life—but at what price?

ALAN D. BEDRICK, MD
Section of Neonatology and
Nutritional Sciences
Department of Pediatrics
University of Arizona
College of Medicine
1501 N Campbell Ave
Tucson, AZ 85724

References

1. Novick LF, Berns D, Stricof R, Stevens R, Pass K, Wethers J. HIV seroprevalence in newborns in New York State. *JAMA*. 1989;261:1745-1750.

2. Lipton SV, Brunell PA. Management of varicella exposure in a neonatal intensive care unit. *JAMA*. 1989;261:1782-1784.

3. Fojaco RM, Hensley GT, Moskowitz L. Congenital syphilis and necrotizing funisitis. *JAMA*. 1989;261:1788-1790.

4. Drugan A, Krause B, Canady A, Zador IE, Sacks AJ, Evans MI. The natural history of prenatally diagnosed cerebral ventriculomegaly. *JAMA*. 1989;261:1785-1787.

5. Chasnoff IJ, Griffith DR, MacGregor S, Dirkes K, Burns KA. Temporal patterns of cocaine use in pregnancy. *JAMA*. 1989;261:1741-1744.

6. Allen DM, Buehler JW, Samuels BN, Brann AW Jr. Mortality in infants discharged from neonatal intensive care units in Georgia. *JAMA*. 1989;261:1763-1766.

7. Nelson NM. But who shall monitor the monitor? *Pediatrics*. 1978;61:663-664.

8. Stahlman M. Implications of research and high technology for neonatal intensive care. *JAMA*. 1989;261:1791.

9. McCormick M. Long-term follow-up of infants discharged from neonatal intensive care units. *JAMA*. 1989;261:1767-1772.

10. Schechner S. For the 1980s: how small is too small? *Clin Perinatol*. 1980;7:135-143.

11. Lucey J. Foreword. In: Gottfried A, Gaiter J, eds. *Infant Stress Under Intensive Care*. Baltimore, Md: University Park Press; 1985;ix.

AJDC Is Moving . . .

As of April 1989, the AJDC editorial office will be located at Tulane University. After April 19, please address all correspondence, manuscripts, and inquiries to Vincent A. Fulginiti, MD, Editor, *AJDC*, Dean's Office, Room 1529, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; (504) 584-1989.

The Editorial Board Speaks . . .

Elizabeth R. McAnarney, MD

Lissa has provided *AJDC* with a perspective on adolescent health issues by her participation in Board activities, her referral of authors and topics to *AJDC*, and her excellent, fair, critical reviews. She remains professor of pediatrics, psychiatry, and nursing at the University of Rochester, NY. Recent accomplishments include winning the Wyeth Visiting Professor Award of the Society for Adolescent Medicine and lectureships at the universities of Arizona, Tucson; East Carolina, Greenville, NC; and British Columbia, Vancouver, Canada, and at the North Shore University Hospital in Manhasset, NY. She has joined the Board of Trustees of the Institute for Pediatric Service of the Johnson & Johnson Co. She remains a thesis committee member for graduate students in nursing and community health and postdoctoral director for the fellowship program in adolescent medicine. She has received research awards for the investigation of various aspects of adolescent pregnancy, from the biologic to the psychologic. She remains an active contributor to the medical literature and has written many chapters in books and, with Melvine Levine, MD, coedited the text *Early Adolescent Transitions*. Her essay below explores one of the most vexing issues in today's world. It is a worrisome issue, that of connectedness for our children, adolescents, and young adults—an issue that affects all of us in some way.

CONNECTEDNESS

Middle age is that stage in life in which we can look back and relate to older generations and look ahead and relate to younger generations. Erikson[1] described this stage as *generativity*, "the concern in establishing and guiding the next generation." As we assume the responsibility of guiding the next generation of children, we might question whether the important connections between and among generations in America are intact. Do our children have a sense of connectedness in their lives so that as they face new challenges they can resolve them by drawing on previous experiences?

Perhaps I believe that connectedness is important for our young people because I grew up in a small village in upstate New York during the post–World War II era, when community residents were connected. To this day, a walk on the streets in this small village results in a warm, Proustian experience; one home reminds me of four decades ago and its regal-appearing inhabitant, who was white-haired, tall, and often attired in a soft, violet dress. She frequently waved as we walked by her home on our way to and from school. Walking by another house, which since has changed families many times, reminds me of two elderly sisters, one of whom supervised my first gardening experience and a premature peek at a fragile carrot. Each of us probably has similar experiences we remember as we integrate the past and the future.

We might question whether life is different now and whether today's children have such experiences, which will become the memory bank of their futures. If life is different now, are our youngsters missing out on the special connections among older relatives, neighbors, and the community's children? Are there any indicators from scientific data that children's lives are less connected than they were in days gone by?

I find the data about some of our nation's families, children, and adolescents worrisome. It is estimated that by 1994 nearly 87% of black youths and 40% of white youths will have spent some part of their childhoods in one-parent homes. Growing up in one-parent homes does not necessarily mean that children will not experience connectedness, but it is known that children from one-parent families do less well in many areas than children from two-parent families. For example, they are more likely to be tardy, truant, and subject to disciplinary action in school. We know that some adolescents and young adults are turning to violence as a means of resolving their distress; accidents, suicides, and homicides are the leading causes of death in the 15- to 24-year-old group.[2] When violence is turned against perfectly innocent victims, does this indicate that we are less connected with others and less caring about others than we once were?

Scientific data indicate that social support and social relationships have salutary effects. Social support, which is largely a result of being connected to others, is classically defined as "information leading the subject to believe he is cared for, loved, esteemed, and a member of a network of mutual obligations."[3] It is believed to modify the negative effects of psychological stress on depression, injuries, schizophrenia, and tuberculosis. Data also indicate that social support may even modify the effects of psychological stress on pregnancy outcome.[4] The exact physiologic and/or psychological mechanisms by which social support ameliorates the adverse effects of stress on outcome are, however, unknown.

We have read recently in *AJDC* about the stress experienced during pediatric residency training. We have also read that support of house staff through flexible scheduling, advisor systems, and retreats is believed to decrease their psychological stress.[5] One hypothesis might be that these creative efforts to develop social support within house officer groups increase the amount of connectedness the young people feel to each other, their patients, and the institutions in which they serve.

Few of us would want to return to times gone by. However, are there lessons from older generations that might help us, in Erikson's terms, to be optimally generative on behalf of our children? It is by integrating the lessons taught to us by both older generations and younger generations that we shall ultimately be most productive.

References

1. Erikson E. Childhood and Society. New York, NY: WW Norton & Co Inc; 1963:267.
2. McAnarney ER. Discontinuity: a dilemma for adolescents. Pediatrics. 1987;80:954-956.
3. Cobb S. Social support as a mediator of life stress. Psychosom Med. 1976;38:300.
4. Rahe RH, Myer M, Smith M, et al. Social stress and illness onset. J Psychosom Res. 1964;8:35-44.
5. Hoekelman RA. Stress experienced during pediatric residency training: its causes, consequences, recognition, and solutions. *AJDC*. 1989;143:177-180.

Articles

The Effect of Weight Control on Lipid Changes in Obese Children

Leonard H. Epstein, PhD; Lewis H. Kuller, MD; Rena R. Wing, PhD; Alice Valoski, MS; James McCurley, MA

• **The effects of weight change on serum lipid changes were assessed in a sample of 56 obese children randomly assigned to family-based behavioral obesity treatment vs controls given no treatment. Fasting serum lipid levels, height, weight, and fitness were measured at program entry and after 6 months of treatment. Children assigned to treatment showed significantly greater relative weight and weight changes than children in the control group, and the weight changes were significantly related to reductions in fasting serum triglyceride and total serum cholesterol levels and increases in high-density lipoprotein serum cholesterol. Results after 5 years of follow-up available for a small sample of treated children showed that a change in relative weight and fitness from 6 months to 5 years was also associated with changes in the high-density lipoprotein level. These results suggest that weight control in obese preadolescent children may be associated with improvement in lipoprotein profiles.**
(*AJDC*. 1989;143:454-457)

Obesity is prevalent in childhood,[1] and obese children are at an increased risk of becoming obese adults.[2-4] Childhood obesity is related to increased total cholesterol and triglyceride levels and decreased high-density lipoprotein (HDL) levels.[5,6] Lipid levels are stable over time,[7] and changes in relative weight are strongly related to lipid changes over 5 years during development.[7,8] Given the relationship between obesity and serum lipid levels, obese children are at risk to become obese adults who have elevated serum cholesterol and triglyceride levels and decreased HDL levels and who are at risk for coronary heart disease.

Given the importance of regulation of body weight during development in preventing obesity and improving serum lipid profiles, surprisingly little is known about the effects of weight regulation on changes in serum lipid levels in preadolescent children. A small, uncontrolled study of the impact of diet and exercise changes on weight loss in 14 preadolescent children showed no changes in total or HDL-cholesterol and a significant increase in triglycerides after 3 weeks.[9] Coates and colleagues[10] found significant decreases in total cholesterol but no significant changes in HDL-cholesterol or triglyceride levels after a 6-month trial. More encouraging results have been reported from our clinical research unit, where we observed significant decreases in serum cholesterol and serum triglyceride levels as well as significant increases in HDL cholesterol after 2 months of weight loss.[11]

Comprehensive treatment for obese children includes diet, exercise, and behavioral skill training for children and their parents in habit change and social reinforcement.[12] We have shown that decreases in relative weight are maintained over a 5-year period using a comprehensive, family-based intervention.[13] The present randomized, controlled outcome study was designed to assess the relationship between weight and serum lipid changes in obese children. The primary goal was to assess the effects of weight change over 6 months on serum lipid changes. Short-term weight changes for the children have been described previously.[14] Almost half of the treated sample studied at 6 months was retested at 5 years, providing an additional assessment of the long-term relationship between weight and serum lipid change.

SUBJECTS AND METHODS

Subjects

Subjects were recruited by newspaper advertisements, fliers distributed by schools, and physician referrals. Entrance criteria for the program were as follows: (1) child's age between 8 and 12 years; (2) at least one child and one natural parent who were more than 20% over ideal weight for age, sex, and height[15,16]; (3) child's triceps skinfolds greater than the 95th percentile for age and sex[17]; and (4) no history of psychiatric contact for the children.

Study Design

Subjects were randomly assigned to one of three treatment groups: (1) diet (n = 18), (2) diet plus life-style and exercise (n = 19), and (3) no treatment–control (waiting list) (n = 19). The treatment methods, which have been extensively tested in our laboratories,[18] were described in detail in a previous report.[14] Briefly, information on diet, exercise, stimulus control, reinforcement, modeling, and contingency contracting was presented to parents and their children in eight weekly sessions followed by four monthly sessions. Diets for children were set between 3800 and 5000 kJ/d and were monitored by a nutritionist (A.V.) to maintain nutrient adequacy. Since decreases in the percentage overweight were not significantly different for the two treatment groups after 6 months (−16.9% and −19.3%) and 5 years (−0.8% and −5.1%), the two treated groups were combined for purposes of evaluating the effects of weight change on serum lipid change. The control group was given treatment after 6 months.

Measurements

Weight, height, fitness, and serum lipid determinations were made prior to treatment and after 6 months for treated and control subjects, and for a limited sample of treated children after 5 years. The percent-

Accepted for publication January 11, 1989.

From the Departments of Psychiatry (Drs Epstein and Wing, Ms Valoski, and Mr McCurley) and Public Health (Dr Kuller), University of Pittsburgh, Pa.

Reprint requests to Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213 (Dr Epstein).

Table 1.—Height, Weight, Percentage Overweight, Fitness, and Serum Lipid Changes From Baseline to 6 Months*

	Treatment Groups (n=35)		Control Group (n=16)		
	Baseline	Change at 6 mo	Baseline	Change at 6 mo	P
Age, y	10.5 (1.3)		10.3 (1.2)		...
% overweight	42.3 (13.6)	−17.4 (10.0)	50.1 (15.6)	−0.8 (8.7)	.001
Height, cm	147.8 (10.1)	+2.8 (1.3)	145.8 (11.2)	+4.3 (1.3)	.001
Weight, kg	56.1 (11.0)	−3.6 (4.0)	56.7 (13.4)	+5.2 (3.0)	.001
Fitness, percentile	33.8 (28.3)	+33.1 (29.0)	32.6 (23.6)	+3.4 (25.1)	.002
Serum cholesterol, mmol/L	4.47 (0.82)	−0.27 (0.47)	4.09 (0.74)	+0.09 (0.50)	.03
Serum HDL,† mmol/L	0.99 (0.20)	+0.20 (0.16)	0.93 (0.21)	+0.06 (0.13)	.007
Serum triglycerides, mmol/L	1.33 (0.58)	−0.55 (0.53)	1.56 (0.69)	−0.12 (0.30)	.01

*All values are mean (SD).
†HDL indicates high-density lipoprotein.

age overweight was calculated in reference to the ideal weight for age, sex, and height,[15] and is the percentage over the ideal weight. Serum samples for serum lipid determinations were collected after a 12-hour fast and stored at −70°C. Total serum cholesterol and serum triglyceride levels were measured by enzymatic methods, and HDL-cholesterol was measured by the heparin-manganese precipitation technique. These assays were performed at the University of Pittsburgh (Pa) Graduate School of Public Health Lipids Laboratory. Only samples collected when subjects were fasting were used for triglyceride analyses. This caused a loss of four subjects for both the 6-month and 5-year samples. The laboratory is a participant in the Centers for Disease Control–National Heart, Lung, and Blood Institute Lipid Standardization Program. Fitness was assessed using a submaximal step test,[19] and percentile rankings using recovery heart rates were calculated based on standardization data.

Statistical analyses of change were completed by use of ANOVA. Relationships among variables were established using Pearson Product-Moment Correlations, with significance levels for all univariate correlation coefficients adjusted using the Bonferroni adjustment to reduce the overall comparison error rate for multiple comparisons. In addition, multiple linear regression models were built to predict serum lipid changes using sex, age, percentage overweight change or weight change, and fitness change as predictors. We used SYSTAT[20] for the statistical analyses. All reported P values were derived from two-tailed tests.

RESULTS

Fifty-one of the 56 original participants completed the 6-month program, with 35 in the treatment groups and 16 in the control group. Nine participants did not have 6-month serum lipid data because they refused venipuncture. Twenty-eight (80%) of the 35 children who completed treatment were reexamined at the 5-year follow-up. Long-term serum lipid data were available for 16 of these children; the other 12 children refused venipuncture.

Table 2.—Pearson Product-Moment Correlation Coefficients for Age, Sex, and Changes in Percentage Overweight, Weight, and Serum Lipid Levels From Baseline to 6 Months

	Pearson Product-Moment Correlation Coefficients*		
	Cholesterol	HDL†	Triglycerides
Age	−.15	.20	−.18
Sex	.20	−.07	.24
% overweight	.43	−.34	.53‡
Weight	.46‡	−.46‡	.60‡
Fitness	−.11	.39	−.29

*n=42 for all the cholesterol and HDL analyses and n=38 for all the triglycerides analyses, with the exception of cholesterol and HDL by fitness, when n=40, and triglycerides by fitness, when n=36.
†HDL indicates high-density lipoprotein.
‡$P<.05$.

Changes at 6 Months

Table 1 shows the mean (SD) values for weight, height, fitness, and serum lipid levels for treated and control children at baseline and after 6 months of treatment. No baseline differences were observed between the treatment and control groups for height, weight, fitness, or serum lipid variables. Analysis of change scores from baseline to 6 months showed significant improvements in weight ($F[1,49]=61.41$, $P<.001$), percentage overweight ($F[1,49]=27.74$, $P<.001$), and fitness levels ($F[1,43]=10.96$, $P=.002$) for treated vs control children. Treated groups had decreases in weight of 3.6 kg and in percentage overweight of 17.4%, while the control group gained 5.2 kg, which was appropriate for growth, as their percentage overweight values remained stable (−0.8%). Fitness improved by about 33 percentile points for the treated children and remained unchanged (+3.4) for the control children.

Significant group effects were observed for the change in serum cholesterol ($F[1,40]=5.31$, $P=.03$), with decreases of 0.27 mmol/L for the treated children and an increase of 0.09 mmol/L for controls. There were significant differences in HDL-cholesterol levels over the 6 months of observation ($F[1,40]=7.99$, $P=.007$), with greater increases in the treated children (+0.20 mmol/L) than in the control children (+0.06 mmol/L). Serum triglyceride

Table 3.—Height, Weight, Percentage Overweight, Fitness, and Serum Lipid Changes in Treated Children at Baseline, 6 Months, and 5 Years*

	Baseline	6 mo	5 y	P†
% overweight	43.2 (12.5)	25.0 (14.9)	39.9 (19.8)	NS
Height, cm	147.6 (10.4)	150.1 (10.4)	166.6 (9.1)	.001
Weight, kg	55.8 (9.5)	51.7 (4.0)	79.8 (14.6)	.001
Fitness, percentile	37.1 (30.1)	63.4 (28.5)	45.1 (30.9)	NS
Serum cholesterol, mmol/L	4.67 (0.76)	4.48 (0.61)	4.77 (0.94)	NS
Serum HDL,‡ mmol/L	0.99 (0.20)	1.22 (0.25)	1.23 (0.33)	.003
Serum triglycerides, mmol/L	1.35 (0.59)	0.79 (0.28)	0.93 (0.45)	.068

*All values are mean (SD). Data are based on the sample available at 5 years. This included 28 children for the height, weight, percentage overweight, and fitness percentile measurements and 16 children for the serum lipid measurements.
†*P* values are for the change between baseline and 5-year values.
‡HDL indicates high-density lipoprotein.

levels decreased significantly over 6 months ($F[1,36]=7.34$, $P=.01$), with greater decreases among the treated children (-0.55 mmol/L) than among the control children (-0.12 mmol/L).

The adjusted correlation coefficients for sex, age, and changes in percentage overweight, weight, and fitness are presented in Table 2. Serum cholesterol, HDL-cholesterol, and serum triglyceride changes were related to changes in weight ($P<.05$). Serum triglyceride change was also related to change in the percentage overweight ($P<.01$). Neither sex nor age was related to any of the serum lipid changes. Multiple linear regression analysis supported these relationships, as the addition of other predictors did not change the relationship between weight and any of the lipid changes.

5-Year Follow-up

Table 3 summarizes the initial, 6-month, and 5-year height, weight, percentage overweight, and serum lipid measurements for participants in the intervention groups followed up at 5 years. No baseline differences were observed in any dependent variables between subjects in the two treatment groups who completed the 5-year follow-up compared with subjects who began treatment but were not measured at 5 years. Since control children were offered treatment after 6 months, no nontreated cholesterol group was available at 5 years. Repeated-measure analysis of variance (baseline, 6 months, and 5 years) showed significant increases in height ($F[1,27]=170.66$, $P<.001$) and weight ($F[1,27]=71.56$, $P<.001$) over the 5 years but no differences in the percentage overweight compared with baseline values. While approximately one third (9/28) of the children were not obese at 5 years, increases in the percentage overweight for another third of the children resulted in the lack of difference in the percentage overweight at 5 years. The HDL-cholesterol level was significantly improved compared with baseline values ($F[1,15]=11.98$, $P=.003$), with these values remaining stable compared with values observed at 6 months.

Adjusted Pearson Product-Moment Correlation Coefficients between sex, age, and percentage overweight and fitness changes between 6 months and the end of intervention showed no significant relationships. This is in part due to the restricted sample size, since the magnitude of the changes suggests similar relationships between weight change and cholesterol and triglyceride levels at 5 years and at 6 months. For example, the percentage overweight change was strongly related to both the total serum cholesterol ($r=.56$) and triglyceride ($r=.42$) levels. Multiple linear regression analyses showed that the combination of changes in percentage overweight and fitness predicted changes in HDL-cholesterol, with the best-fitting equation of HDL-cholesterol as follows: HDL-Cholesterol $= -7.64 + (0.85 \times$ Percentage Overweight Change$) - (0.17 \times$ Fitness Change). The significance levels for percentage overweight and fitness change were .021 and .008, respectively (adjusted multiple $r=.44$, $P=.02$). The best-fitting equation for triglycerides included age and fitness change: Triglycerides $= -370.00 + (32.714 \times$ Age$) + (0.97 \times$ Fitness Change). The significance levels for age and fitness were .028 and .024, respectively (adjusted multiple $r=.67$, $P=.015$).

COMMENT

The family-based treatment methods presented here were effective in decreasing the percentage overweight over 6 months of treatment, consistent with other reports from our clinical research unit.[13] Changes in weight were associated with significant decreases in total serum cholesterol and serum triglyceride levels and a significant increase in HDL-cholesterol after 6 months of treatment. Correlational analyses indicated that the magnitude of serum lipid change during treatment was significantly related to relative weight change.

Examination of the relationship between relative weight, fitness, and serum lipid change at 6 months suggested that while changes in relative weight and fitness were related ($r[51]=.53$, $P<.01$), the changes in weight were significantly related to serum lipid changes, while fitness changes were not. This finding is consistent with the research by Fripp and colleagues,[21] who showed that relative weight was a more important determinant of serum lipid levels than fitness. Likewise, Thorland and Gilliam[22] demonstrated that, when children did not differ in weight, more active children had significantly lower triglyceride levels than less active children, but there were no differences in total serum cholesterol or HDL levels.

The lack of an untreated control group at 5 years limits our understanding the of the effect of long-term weight control on serum lipid levels. Based on epidemiologic research,[8] if the obese children continue to accumulate body fat and increase their relative weight, they would be expected to have increases in serum cholesterol and serum triglyceride levels and a decrease in HDL-cholesterol. Cross-sectional normative lipid changes would predict decreases in total serum cholesterol, decreases in HDL-cholesterol, and increases in triglyceride levels.[23] In the present study, HDL and serum triglyceride levels showed large improvements over 5 years, while serum cholesterol was unchanged. Changes in the percentage overweight and fitness from the end of treatment to the 5-year measurement were strongly related to HDL-cholesterol changes, while triglyceride changes were a function of age and fitness change. Thus, from the end of treatment to 5 years, fitness change was a predictor of change in HDL-cholesterol in addition to relative weight change, and fitness change was a more important predictor of triglyceride change than was relative weight. Given the limitations in generalizing from the small sample available at 5 years, fitness seemed to exert a greater influence on the serum lipid measures at 5 years than at 6 months. While there is mixed experimental support for the independent effect of exercise on serum lipid changes,[24,25] weight change is an important influence on fitness change over 5 years,[26] and weight regulation may be an important mechanism in the improvement of fitness, increases in HDL levels, and decreases in serum triglyceride levels.

In conclusion, the results of the intervention study reported here support the observations made in descriptive population studies of relative weight and serum lipid change in children.[7,8] The weight loss program reliably reduced weight in overweight children, reduced total serum cholesterol and serum triglyceride levels, and increased HDL-cholesterol during the treatment period. After 5 years of follow-up, during a period of growth, changes in relative weight and fitness from the end of the treatment program to the 5-year visit were related to changes in serum lipid levels. This suggests that weight control may have long-term benefits on serum lipid tracking in children and adolescents. Further work is needed to document the long-term effects of weight regulation on serum lipid levels in children and to identify the mechanisms of these changes.

We thank Geoffrey Block, MD, MPH, for assisting on the 5-year follow-up and initial preparation of the manuscript, Margaret Bates, PhD, for serum lipid analyses, and Randi Koeske, PhD, for assistance in data analysis.

References

1. Gortmaker SL, Dietz WH, Sobol AM, Wehler CA. Increasing pediatric obesity in the United States. *AJDC*. 1987;141:535-540.
2. Abraham S, Collins G, Nordsieck M. Relationship of childhood weight status to morbidity in adults. *Public Health Rep*. 1971;85:273-284.
3. Abraham S, Nordsieck M. Relationship of excess weight in children and adults. *Public Health Rep*. 1960;75:263-273.
4. Stark O, Alkins E, Wolff OH, Douglas DWB. Longitudinal study of obesity in the National Survey of Health and Development. *Br Med J*. 1981;283:13-17.
5. Laskarzewski P, Morrison JA, Mellies MJ, et al. Relationships of measurements of body mass to plasma lipoproteins in school children and adults. *Am J Epidemiol*. 1980;111:395-406.
6. Smoak CG, Burke GL, Webber LS, Harsha DW, Srinivasan SS, Berenson GS. Relation of obesity to clustering of cardiovascular disease risk factors in children and young adults: the Bogalusa Heart Study. *Am J Epidemiol*. 1987;125:364-372.
7. Webber LS, Cresanta JL, Voors AW, Berenson GS. Tracking of cardiovascular disease risk factor variables in school-age children. *J Chronic Dis*. 1983;36:647-660.
8. Freedman DS, Burke GL, Harsha DW, et al. Relationship of changes in obesity to serum lipid and lipoprotein changes in childhood and adolescence. *JAMA*. 1985;254:515-520.
9. Widhalm K, Maxa E, Zyman H. Effect of diet and exercise upon the cholesterol and triglyceride content of plasma lipoproteins in overweight children. *Eur J Pediatr*. 1978;127:121-126.
10. Coates TJ, Jeffery RW, Killen JD, Danaher BG. Frequency of contact and monetary reward in weight loss, lipid change, and blood pressure reduction with adolescents. *Behav Ther*. 1982;13:175-185.
11. Epstein LH. Family-based treatment for pre-adolescent obesity. In: Wolraich M, Routh DK, eds. *Advances in Developmental and Behavioral Pediatrics*. Greenwich, Conn: JAI Press Inc; 1985:1-39.
12. Epstein LH, Wing R. Behavioral treatment of childhood obesity. *Psychol Bull*. 1987;101:331-342.
13. Epstein LH, Wing RR, Koeske R, et al. Long-term effects of family-based treatment of childhood obesity. *J Consult Clin Psychol*. 1987;55:91-95.
14. Epstein LH, Wing RR, Koeske R, Valoski A. The effects of diet plus exercise on weight change in parents and children. *J Consult Clin Psychol*. 1984;52:429-437.
15. Jelliffe DB. *The Assessment of the Nutritional Status of the Community*. Geneva, Switzerland: World Health Organization; 1966.
16. 1983 Metropolitan height and weight tables. *Stat Bull Metropolitan Life Insur Co*. 1983;64:2-9.
17. Garn SM, Clark DC. Trends in fatness and origins of obesity. *Pediatrics*. 1976;54:443-456.
18. Epstein LH, Wing RR, Valoski A. Childhood obesity. *Pediatr Clin North Am*. 1985;32:363-379.
19. Montoye HJ. *Physical Activity and Health: An Epidemiological Study of an Entire Community*. Englewood Cliffs, NJ: Prentice-Hall International Inc; 1975.
20. Wilkinson L. *SYSTAT: The System for Statistics*. Evanston, Ill: SYSTAT Inc; 1986.
21. Fripp RR, Hodgson JL, Kwiterovick PO, Werner JC, Schuler HG, Whitman V. Aerobic capacity, obesity, and atherosclerotic risk factors in male adolescents. *Pediatrics*. 1985;75:813-818.
22. Thorland WG, Gilliam TB. Comparison of serum lipids between habitually high and low active pre-adolescent males. *Med Sci Sports*. 1981;13:316-321.
23. Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovick P, Rifkind B. Lipid and lipoprotein distributions in white children 6-19 yr: the lipid research clinics program prevalence study. *J Chronic Dis*. 1981;34:27-39.
24. Lipson LC, Bonow RO, Schaefer EJ, Brewer HB, Lindgren FT. Effect of exercise conditioning on plasma high density lipoproteins and other lipoproteins. *Atherosclerosis*. 1980;37:529-538.
25. Huttenun JK, Lansimies E, Voutilainen E, et al. Effect of moderate physical exercise on serum lipoproteins. *Circulation*. 1979;60:1220-1229.
26. Epstein LH, Wing RR, Valoski A, DeVos D. Long-term relationship between weight and aerobic-fitness change in children. *Health Psychol*. 1988;7:47-54.

Quotables

Skepticism: *It is sometimes taken as a matter of course that skepticism is the highest flower of the scientific spirit. This thesis might be admitted to have an aspect of truth if it did not so often cover a mere automatic means of protecting ourselves against the painful eruption of new ideas.*

W. TROTTER

Efficacy of a Nonrestricted Fat Diet in Patients With Cystic Fibrosis

Elisabeth Luder, PhD; Meyer Kattan, MD; John C. Thornton, PhD; Kathleen M. Koehler, PhD; Richard J. Bonforte, MD

• We sought to determine if an increased oral intake with a noninvasive nutrition program in patients with cystic fibrosis could influence growth, weight gain, and pulmonary function. Thirty-seven patients, aged 2 to 27 years, were instructed to consume a nonrestricted fat diet during an intervention period of 4 years. The results showed that patients increased the mean energy intake significantly to a level of more than 120% of the recommended daily allowance. The enhanced intake resulted in significant weight gain. Pulmonary function (forced expiratory flow$_{25\%-75\%}$) deteriorated during the 2-year preintervention period but stabilized during the 4-year intervention period. Both male and female patients were able to maintain their established height and weight scores during adolescence. The recommendation for a high-energy diet with no restrictions placed on the fat intake and the control of the steatorrhea by administration of an optimal enzyme dosage is supported by our data. Individualized nutritional counseling should be attempted before implementing invasive nutritional intervention programs.

(*AJDC*. 1989;143:458-464)

Nutritional status is related to the clinical course for patients with cystic fibrosis. (CF)[1,2] A relationship between weight loss and deterioration in pulmonary function in patients with more advanced disease has been suggested.[3,4] In addition, nutritional deficits can exist in very young infants with unsuspected CF.[5] Because there are some indications that improved nutrition can favorably influence the course of pulmonary disease and long-term outcome in patients with CF,[2,6] a goal of therapy should be to correct nutritional inadequacies in patients with CF as early as possible.

To improve the undernutrition brought on by anorexia, inefficient absorption of nutrients, and increased energy requirements induced by the added stress of pulmonary infection,[4] the traditional approach has been directed toward correcting maldigestion and increasing the total energy intake. However, studies have documented that the mean energy intake of patients with CF is only 80% of that of the normal population.[7] Hydrolyzed diets administered orally[8] or by tube feeding[9] and total parenteral nutrition[10,11] have resulted in increased energy intake and improvements in height, weight, and activity levels. Investigators correlated weight gain with changes in pulmonary function over periods of 1 to 12 months and obtained equivocal results.[9-11] In addition, most of the apparent benefits derived during the intervention periods were lost 12 months after treatment was discontinued. Palatability of supplemental diets and the invasive nature of these interventions are major drawbacks and can affect life-style.[8,9]

In recent years there has been a growing tendency to use invasive nutrition programs, such as total parenteral nutrition and intragastric feedings, to maintain weight in patients with CF. We therefore conducted a study to establish whether a noninvasive nutrition intervention program, consisting of a nonrestricted fat diet, emphasizing a high energy intake and administration of an optimal pancreatic enzyme replacement dosage, could enhance the nutritional and pulmonary status of patients with CF. We specifically addressed the following questions for evaluating any effect on a long-term basis: (1) Can patients with CF increase their oral mean energy intake to 120% of the recommended daily allowance (RDA)[12]? (2) If patients with CF can increase their energy intake, will it affect growth and specifically weight gain? (3) If increased energy intake and weight gain is achieved, will it affect pulmonary function?

PATIENTS AND METHODS

Patient Selection

Thirty-seven patients (aged 2 to 27 years) were studied over a 6-year period until June 1984. At the beginning of the study, there were 8 patients ranging in age from 2 to 5 years, 12 patients from 6 to 10 years, 9 patients from 11 to 18 years, and 8 patients older than 18 years. The study was divided sequentially into a retrospective preintervention and a prospective intervention period. The preintervention period lasted 2 years, and the nutritional counseling period (intervention) lasted 4 years. Patients acted as their own controls.

The subjects were patients with documented CF followed up at two pediatric pulmonary centers (New York, n = 17; New Mexico, n = 20). To assure the commitment of the patient and the family to comply with this long-term nutrition intervention project and to control for the quality of the medical care, only patients who had been regularly attending the clinic (three visits a year) during the preintervention period were selected for the nutrition counseling program. Forty-one patients qualified for this study, and 37 patients (22 male, 15 female) completed the 6-year study period. Two patients moved out of the centers' areas and two patients died. During the study period of 6 years, all patients received routine care, including physiother-

Accepted for publication December 13, 1988.

From the Jack and Lucy Clark Department of Pediatrics, Mount Sinai School of Medicine, New York, NY (Drs Luder, Kattan, Thornton, and Bonforte), and the Department of Pediatrics, University of New Mexico Albuquerque, NM (Dr Koehler).

Presented in part at the 26th Annual Meeting of the Cystic Fibrosis Club, Anaheim, Calif, May 16, 1985.

Reprint requests to Jack and Lucy Clark Department of Pediatrics, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029-6574 (Dr Luder).

apy, enzyme replacement (for the 36 patients with pancreatic exocrine deficiency; 29 patients received enteric-coated products), vitamin supplementation, and antibiotics for infection. The medical status of the patients and the therapeutic regimens were comparable in the two pediatric pulmonary centers. The methods for measurements of variables, data collection, and counseling were based on published standards.[13-15] The nutritional counseling was conducted according to Bandura's method[13] by the same two nutritionists/registered dietitians during the entire counseling period. Specific data on age, sex, height, weight, and pulmonary function were recorded at the beginning of the study period (baseline or year 0) and six times afterward at yearly intervals. Energy intake was recorded at the start of nutrition intervention and during each subsequent year of counseling.

Nutritional Intervention

During the preintervention period (2 years) the consumption of a diet consisting of approximately 30% fat was recommended. Patients were provided with written instruction on helpful hints for achieving this diet and received information on foods permitted and restricted on the special diet (sample meal: chicken with skin removed, boiled potatoes, vegetables, skim milk, and two capsules of pancreatic enzyme supplements). Pancreatic enzyme supplements were prescribed for meals and snacks.

During the intervention period we aimed to achieve through counseling an increased energy intake that could be sustained on a long-term basis and thereby lead to normal weight gain and development in patients with CF. The target level for mean energy intake was set at 120% of the RDA and 20% of energy from protein was recommended. No restriction was placed on the intake of fat. In addition, patients received general nutritional guidelines with the recommendation to eat a variety of foods and to choose from the four major food groups (dairy, meat, fruit and vegetable, and grain and cereal). No restrictions were imposed on the intake of specific foods or nutrients.

To achieve an increased energy intake, patients were encouraged to select energy-dense meals and snacks (sample meal: fried chicken, french fries, vegetables, milk shake, and five capsules of pancreatic enzyme supplements). To tolerate these meals, patients adjusted the pancreatic enzyme replacement dosage according to the fat content of meals and snacks. Optimal dosage was determined by chemical analysis of fecal fat or by the response of the patient with respect to weight gain and stool history. Specific dietary advice was developed according to the requirements of each patient[14] based on the following: (1) current nutritional assessment (anthropometric data, laboratory data, and diet history), (2) maldigestion/malabsorption, (3) glucose intolerance, (4) chronic and/or acute infection, (5) pulmonary function, and (6) family support. For each patient a meal plan was developed in cooperation with the patient and/or family. The plan was tailored to the patient's needs and wishes, and emphasis was placed on practicality, ease of implementation, and acceptance.

In addition to the routine evaluation given during a scheduled clinic visit at 3-month intervals, nutritional counseling was provided by the nutritionist. The counseling sessions included the measurement of height and weight, calculation of energy intake, and discussion of the individually designed diet plan (20 to 30 minutes). Adherence to the plan was assessed by a 24-hour dietary recall to determine the energy intake per day and by the achievement of expected weight gain and growth for the younger patients. If the goals were not achieved, the underlying cause was investigated to determine if failure was accompanied by increased severity of pulmonary infection or decreased energy and/or enzyme intake as documented by the 24-hour dietary recall. If indicated, changes in the diet were made, again with patient and/or family participation.

The 24-hour recall was selected as the main teaching tool. The recall method allowed for the educational exchange between the counselor and the counselee. Both were able to interpret the extent to which the prescribed goals were accomplished and determined if adjustments in the plan were indicated. Information elicited was used as a reference point from which each participant began to learn. For example, the nutritionist pointed out that a cup of ice cream contains 1071 kJ and 14 g of fat, whereas a cup of fruit ice has only 441 kJ and no fat. With the ice cream, the patient had to take an enzyme supplement; this was not necessary with the fruit ice.

A height and weight curve was plotted and reviewed with the patient during each clinic visit. The growth chart and the 24-hour dietary recall were used as self-evaluation tools for the patients.

Energy Intake

At the start of the intervention, the dietary intake was calculated from one 24-hour recall and one 3-day food record. For each year during the counseling period, the dietary intakes were obtained from four 24-hour recalls and one 3-day food record. During the 24-hour recall, interview participants were asked to recall actual food and beverage consumption during the preceding 24 hours. Data on generic and brand names and methods of food preparation, as well as portion size of each reported food using three-dimensional food models, were recorded. For the 3-day food record, participants recorded all food and beverage intake for 3 days (2 week days and 1 weekend day). Before record keeping, patients were instructed in the measurement of portion sizes. Each record was subsequently clarified by the nutritionist during clinic visits, using the three-dimensional food models. From the dietary records the energy intake was calculated according to food value tables from the US States Department of Agriculture.[16]

Energy intake per patient was determined by obtaining the arithmetic mean from seven daily dietary records for each year during the counseling period (four 24-hour recalls and one 3-day food record). These diet records may provide valid assessment of an individual's intake.[15] Mean energy intake expressed as a percentage of the RDA of energy, specific for age and sex for normal population,[12] was recorded at the start of intervention and during each subsequent year of counseling. Mean energy intake of the study group was compared with published normative data.[7]

Height and Weight Measurements

Stature or height and weight measurements were taken by the nutritionist at each clinic visit. Height and weight measurements were standardized for age and sex for statistical comparison in two ways. One way used z scores expressed as $(X-\bar{X})/\mathrm{SD}$, where X is the subject's measurement, $\bar{X}$ is the mean standard for age and sex, and SD is the SD of the $\bar{X}$, based on reference standards from the national population of patients with CF[17] and the normal population (National Center for Health Statistics, Hyattsville, Md).[18,19] In the second approach, patients were ranked by their percentile score into six ordered groupings as follows: 1, lower than 5%; 2, 5% to 25%; 3, 26% to 50%; 4, 51% to 75%; 5, 76% to 95%; and 6, higher than 95%. These data were analyzed both as ranks and average percentile scores.

The Cystic Fibrosis Foundation, Bethesda, Md, maintains a database and the height and weight standards were derived from 13 000 patients with CF from birth to 31.5 or more years of age.[17] The National Center for Health Statistics data were based on measurements of children from birth to 18 years and weight and height measurements of adults 18 to 74 years of age.[18,19] It is well known that patients with CF have a different growth progress from that in the normal population. The comparison with the National Center for Health Statistics data was made to evaluate whether there was any change in the trend of growth in patients with CF as reported in 1975.[20]

Each subject was awarded a z score from CF data and also from National Center for

Health Statistics data, for each measurement. Growth rates and weight changes of the study patients were expressed as the changes in z scores between the points of evaluation. If the z scores became more negative when compared with norms, it signified growth retardation or inadequate weight gain or weight loss. If the z scores became less negative or positive, it denoted improved growth or weight gain. With standard scores (z scores), progress of patients at different ages and sexes can be compared on the same scale. Each subject also received a percentile score as noted above.

Assessment of Pulmonary Function

In the study group, assessment of pulmonary function was obtained in patients 6 years of age or older. Twenty-four patients had valid tests for the entire period. Spirometry was performed with a water-sealed spirometer (Collins, Braintree, Mass) according to the standard recommendations,[21] and the results were expressed as a percentage of the predicted value.[22] We report the forced expiratory flow in the middle half of the vital capacity (forced expiratory flow $[FEF]_{25\%-75\%}$) because it is a sensitive index of airway obstruction in CF.[23] Based on published data, a decline of 8% per year was expected.[24]

Body Mass Index

Body mass index was determined by dividing weight in kilograms by height in meters squared.[25] An index of less than 15 may be considered as the earliest sign of malnutrition in children.[26] Weight/stature^2 is independent of age, and the index may therefore be employed to monitor the progress of nutrition intervention in all patients with CF. During the study, all subjects were free of fluid retention. The index values obtained from the subjects were compared with race- and sex-specific reference values derived from the normal population.[25]

Statistical Tests

Hotelling's T^2 test, the nonparametric Friedman two-way ANOVA, and the χ^2 test were used to analyze the data.[27] The energy intake, height, weight, and pulmonary function of the subjects were measured at several times during the course of the study. These results were analyzed using multivariate repeated measures methods (Hotelling's T^2).

The usual univariate repeated measures ANOVA requires that the variances at each time be equal, and even more restrictively, that the covariances across all combinations of time points be equal. The multivariate Hotelling's T^2 does not require these assumptions but does assume normality. Because of the assumption of normality, the results were verified with the nonparametric Friedman ANOVA. The multivariate Hotelling's T^2 tests the null hypothesis that the measures are all equal at all times. When this hypothesis was rejected, then a Scheffé-type multiple comparison test was used to compare selected times.[27,28] The significance level was set at .05 for all tests. Statistical calculations were performed with the Systat[29] statistical program.

RESULTS

The age range of the 37 subjects at the beginning of the investigation was from 2 to 27 years, with a mean (SD) age of 10.9 (7.64) years for male patients and 12.3 (7.53) years for female patients. Data of female patients for energy intake, body mass index, and pulmonary function were comparable to the values of male patients over time. In addition, the standardized increments in energy intake and weight gain were comparable among the age groups.

Energy Intake

The patients who received nutritional counseling on a nonrestricted fat diet had a significantly higher mean energy intake over time when compared with an expected intake of 80% RDA from published normative data[7] (Hotelling's $T^2 = 148.39$, $F[5,32] = 26.38$, and $P < .0001$). Furthermore, in each intervention year a statistically significant increase in mean energy intake was achieved, reaching the target level of 120% RDA (Hotelling's $T^2 = 110.75$, $F[4,33] = 25.38$, and $P < .0001$) (Table 1). At the end of the intervention period, 22 patients had an energy intake of more than 120% of RDA, 8 patients had an intake between 110% to 120% of RDA, 3 patients had an intake between 100% to 109% of RDA, and 4 patients had an intake less than 100% of RDA.

One 24-hour dietary recall per patient was analyzed for the fat and protein content of the diet at the beginning of the intervention and after 2 and 4 years of counseling. For the group, the mean percent of energy intake from fat was 31.5%, 37.6%, and 39.3%, respectively. The mean percent of energy intake from protein was 20.8%, 17.6%, and 19.2%, respectively.

Height and Weight

Serial z scores for height and weight are shown in Table 2 and Fig 1. Analysis was also done for height scores limited to children aged 18 years or less at entry for three time points (baseline, start of intervention, end of intervention). There was no significant difference between the study group and the national population of patients with CF in height gain over time (Hotelling's $T^2 = 5.57$, $F[7,30] = .66$, and $P = .70$). Use of percentiles, ranks, or restricting the sample to children age 18 years or less did not change the result. The average percentiles were 56.5% at baseline, 56.5% at the start of intervention, and 61.0% at the end of intervention.

When weight measurements of the study group were compared with those from the national population of patients with CF,[17] the values of the intervention group were significantly higher than the values of the population with CF (Hotelling's $T^2 = 21.56$, $F[7,30] = 2.57$, $P = .03$). Scheffé's multiple comparison procedure indicated that weight significantly increased above the preintervention levels ($P < .05$). The increase in weight appears in treatment years 3 and 4 but does not achieve statistical significance until the fourth year. Average percentile scores increased from 50.3% before intervention to 59.1% at the end of intervention ($F[1,36] = 9.84$, $P = .003$).

When height and weight measurements of the study patients were compared with National Center for Health Statistics reference data,[18,19] the values of the study group were approximately 1 SD below the values of the normal population during the entire study period. There was no significant change in the mean z score throughout the study when the patients were divided into age groups (2 to 5 years, 6 to 10 years, 11 to 18 years, and older than 18 years). (For height: Hotelling's $T^2 = 59.67$, $F[7,30] = 7.10$ and $P < .0001$; for weight: Hotelling's $T^2 = 83.12$, $F[7,30] = 9.90$, and $P < .0001$.)

Pulmonary Function

In the preintervention period the decline in pulmonary function in our subjects ($FEF_{25\%-75\%}$, 65.5% to 56.3%) was at a similar rate as observed in the previously published data.[24] During the intervention period, pulmonary function values remained at the same level ($FEF_{25\%-75\%}$, 56.3% to 59.5%) as shown in

Table 1.—Energy Intake, Body Mass Index, and Pulmonary Function of Intervention Group

	Energy Intake, % of Recommended Daily Allowance* (n=37)			Body Mass Index, kg/m²† (n=37)		Pulmonary Function, Forced Expiratory Flow $_{25\%-75\%}$, % Predicted (n=24)		
	Year	Mean (SD)	Range	Mean (SD)	Range	Year	Mean	Range
Baseline	0	. . .	. . .	17.1 (2.3)	14.0-23.7	0	65.5	6-127
Preintervention	1	. . .	. . .	17.0 (2.0)	14.3-22.7	1	64.0	9-128
	2‡	93.6 (16.9)	63-130	16.9 (2.3)	14.1-24.1	2‡	56.3§	6-121
Intervention	3	108.6 (20.0)	67-161	17.6 (2.6)	14.0-24.2	3	59.1	5-130
	4	114.2 (20.6)	74-166	17.7 (2.5)	13.8-22.9	4	58.3	7-140
	5	119.4 (20.5)	81-181	18.1 (2.6)	14.3-23.8	5	55.2	7-132
	6	125.8 (24.1)	88-214	18.8 (2.5)	14.5-24.3	6	59.5	6-141

*$P<.001$, increase in energy intake for each year of intervention.
†$P<.001$, increase in body mass index for each year of intervention.
‡Nutrition counseling started at the end of year 2.
§$P<.01$, decrease in forced expiratory flow, year 2 of preintervention. There were no significant changes during all other years of pulmonary function.

Table 1. The observed decline during the study period of 6 years was 6 percentage points compared with an expected 25.8 percentage points based on the previously published data. The difference was significant (Hotelling's $T^2=19.80$, $F[6,18]=2.58$, and $P=.05$). Figure 2 shows that pulmonary functions declined in a parallel fashion to that expected in the 2 years before the intervention,[24] but stabilized thereafter.

Body Mass Index

There was a slight decline in body mass index during the preintervention period. During the nutritional counseling period, a significant increase in mean body mass index was observed (Hotelling's $T^2=56.32$, $F[6,31]=8.08$, $P<.001$) (Table 1).

Body mass index values of the counseling group were compared with race- and sex-specific reference values derived from normal population data to obtain percentile levels.[25] At the beginning of the intervention period, 65.5% of study patients were at or below the 25th percentile, 21.6% were between the 26th and 50th percentile, and 12.7% were above the 50th percentile. At the end of the 4-year intervention period, 37.5% were in the first quartile, 28.1% were in the second quartile, and 34.4% were above the 50th percentile. The change in quartile distribution was significant ($\chi^2[2]=18.46$, $P<.001$).

Table 2.—Standardized Height and Weight (z Scores) of Intervention Group Compared With Normal Values of Patients With Cystic Fibrosis*

	Year	Height, z Score†	Weight, z Score‡
Baseline	0	0.0010 (0.69)	0.0760 (0.70)
Preintervention	1	−0.0459 (0.57)	0.0091 (0.85)
	2§	−0.0303 (0.59)	−0.0308 (0.99)
Intervention	3	−0.1318 (0.72)	0.0479 (0.88)
	4	−0.0385 (0.64)	0.0052 (0.68)
	5	−0.0290 (0.71)	0.1022 (0.74)
	6	−0.0199 (0.65)	0.2447 (0.85)

*z scores are given as means (SDs).
†The difference from cystic fibrosis reference population for each year during the study was not significant.
‡$P<.03$, increase in weight compared with cystic fibrosis reference population.
§Nutrition counseling started at end of year 2.

Relationship Between Pulmonary Function, Energy Intake, and Weight Gain

For the 24 patients with valid pulmonary function tests, the following changes were observed. At the start of the nutrition intervention period, 6 patients had pulmonary function values ($FEF_{25\%-75\%}$) of less than 30% predicted, 6 patients had values between 30% and 50%, 1 patient had values between 51% and 65%, and 11 patients had values of more than 65% predicted. At the end of the 4-year intervention period, 8 patients had values of less than 30% predicted, 4 patients were between 30% and 50%, 2 patients were between 51% and 65%, and 10 patients had values of more than 65% predicted.

Of those 24 patients, at the end of the 4-year counseling period, only 3 patients (one in each group, except the group of patients with values of 51% to 65%) had a negative change in the z score for weight when compared with the normal population data.[18,19] All patients gained weight, irrespective of the severity of the pulmonary disease, but only these 3 patients were not able to maintain the z score at the expected level.

At the end of the counseling period, the level of energy intake was compared with the level of pulmonary function in those 24 patients. Six patients with $FEF_{25\%-75\%}$ levels of less than 30% and 6 patients with levels of higher than 65% had an energy intake of above 120% of RDA. In each pulmonary function

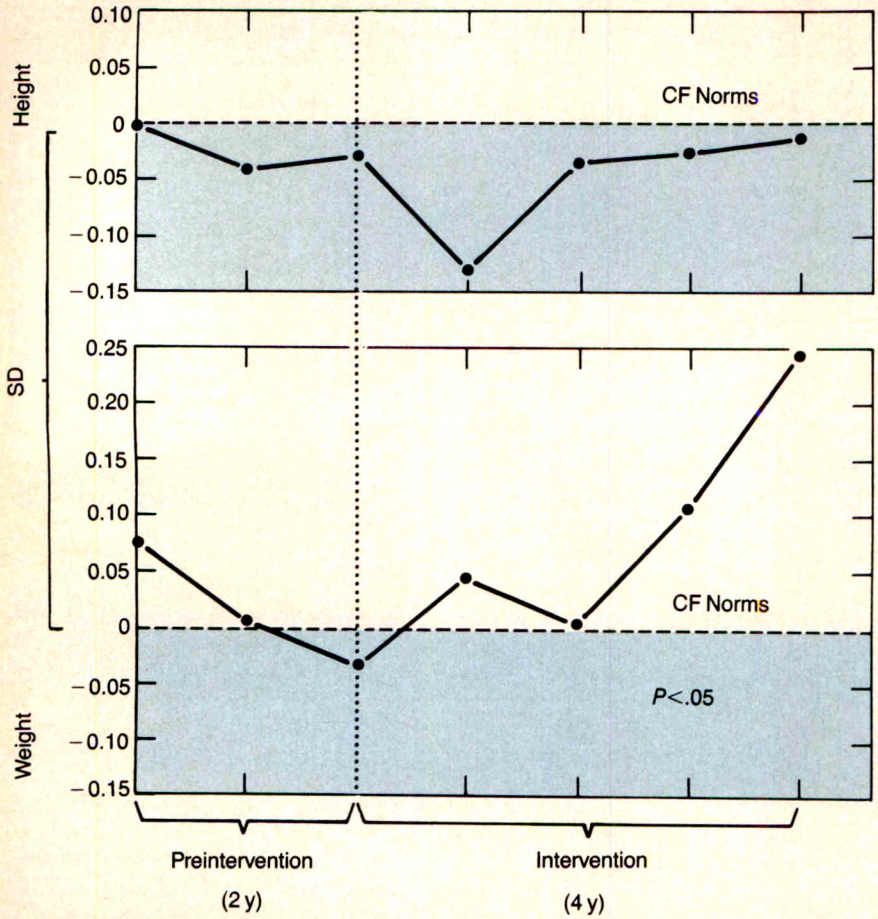


Fig 1.—Standardized height and weight scores compared with national population of patients with cystic fibrosis (CF).

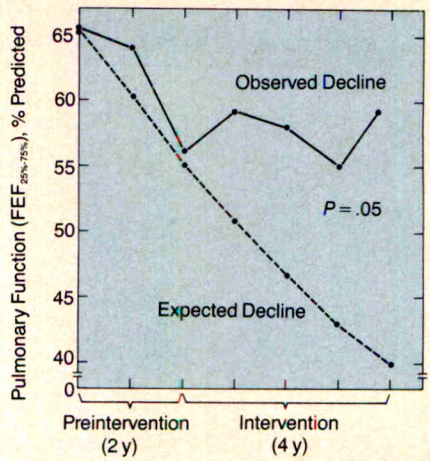


Fig 2.—Pulmonary function during the preintervention and intervention periods compared with the expected decline. $FEF_{25\%-75\%}$ indicates forced expiratory flow.

group, various levels of energy intake were documented for the remaining 12 patients. By observing the progress of individual patients, with each successive year of counseling, the energy intake increased in linear fashion. Patients with lower energy intake at initial evaluation improved but stayed at the lower level. Patients with higher intake at initial evaluation increased their energy intake even further. For the 15 patients who cooperated with the fat absorption study, the absorption rate was between 85% and 92%. Malabsorption was not found to be different among the various levels of energy intake and pulmonary function groups. These results indicate a marked variability in the energy requirements of individual patients to achieve normal weight gain.

COMMENT

Our data demonstrated that with long-term nutrition intervention, a mean energy intake of greater than 120% of the RDA can be achieved and a weight gain significantly above that of the national population of patients with CF can be sustained for all patients, irrespective of the severity of the pulmonary disease. In addition, mean pulmonary function values did not deteriorate as rapidly during the nutritional counseling period.

Our study provides a much longer follow-up than previous reports, allowing an evaluation of the long-term effects of a nonrestricted fat diet on growth and weight gain in patients with CF. The results documented that, with nutritional counseling and close monitoring of a high energy food intake (38% to 40% fat), patients with CF can reach and maintain a mean energy intake of greater than 120% of RDA. Such an intake can result in appropriate rates of weight gain and improvements in body mass index values; however, a wide range of energy intake was observed at all levels of pulmonary function. The findings are in agreement with those of other reports[30-32] that showed that weight gains in patients with CF were seen when energy intake was greater than 115% of RDA. Two programs achieved this intake with nasogastric supplementation.[30,31] The third study[32] promoted normal growth with dietary counseling and high-energy supplementation in eight patients, but the follow-up period lasted only 1 year.

Changes in height among the study patients were not significant when compared with age- and sex-specific norms based on 13 000 patients with CF nationwide.[17] Compared with the normal population data (from the National Center for Health Statistics), height stayed at the same SD below the mean during the entire study period. Among children with CF, significant increases in height have been documented in studies with younger patients with less severe chronic pulmonary disease.[10,31] In studies involving older patients with more advanced chronic pulmonary disease, no significant increases in height were achieved.[11,20]

Weight scores declined during the preintervention period. With nutrition intervention, the trend was reversed and significant gains in weight were achieved when compared with the CF reference group. Furthermore, when compared with the normal population (National Center for Health Statistics

data), the study patients maintained their weight of 0.8 SD below the normal population mean during the entire study period. These results are in contrast to those in the report of Berry et al[20] from 1975 where there was a gradual decline in weight gain after 8 years of age.

Gurwitz et al[3] reported lower scores for weight and pulmonary function for female adolescents than for male adolescents. Their investigation showed that for female patients, body mass index, which is a reflection of weight status, was comparable with that for male patients over time. It appears, therefore, that both male and female patients with CF are able to maintain their established weight scores during adolescence.

Weight gain in patients was observed by other researchers. However, follow-up evaluations in these studies documented that most of the weight gain derived during intervention with total parenteral nutrition, enteral alimentation, or artificial diet were lost in 6 to 12 months after discontinuing treatment.[8,9,11] In this study, patients were following the established weight pattern 1 year after the completion of the intervention. However, two counseling sessions were provided to each patient during the year.

Protein-energy malnutrition may adversely affect the course of pulmonary disease in patients with CF.[11,31] In our study patients, pulmonary function declined at a similar rate to previously published data during the preintervention period.[24] With nutrition intervention, the progressive deterioration was halted and mean $FEF_{25\%-75\%}$ values stabilized during the counseling period of 4 years. In short-term studies (6 to 12 months) with invasive alimentation programs, pulmonary function remained stable but did not show any improvement.[6,30] Improvements in pulmonary function were reported by Shepherd et al[10,31] in two investigations. In the first study, improvements were in response to 18 to 23 days of parenteral nutrition[10]; however, intravenous antibiotics were administered during this period, making it difficult to evaluate the contribution of parenteral nutrition. In a subsequent study, Shepherd et al[31] reported a significant reversal of the deterioration in pulmonary function in 10 patients receiving, in addition to the ad libitum food intake, a 1-year course of nocturnal nasogastric supplements. The measured intake during this period was 120% to 140% of RDA for protein and energy, an equivalent energy intake as reported in our investigation. Thus, the findings of our investigation provide additional data to studies suggesting that nutritional factors may have an influence on the course of pulmonary disease.[3,31,33,34]

Although these investigations regarding pulmonary status show positive results, randomized, prospective controlled studies are necessary to confirm unequivocally the influence of increased energy intake on the progression of chronic lung disease. Nevertheless, our data demonstrate that energy intake can be enhanced and weight gain sustained for many years. In addition to these objective criteria, the psychological benefits of a nonrestricted diet should not be disregarded especially in patients who try to lead a normal adolescent life-style.

Since nutritional deficits may exist before 2 months of age in some infants with CF,[5] it would seem logical that nutritional intervention should be provided to patients starting at the time of diagnosis and continued as part of the routine therapeutic intervention. The patients in our study tolerated the liberalized diet well. The recommendation for a high-energy diet with no restrictions placed on the fat intake, and the control of steatorrhea by administration of an optimal enzyme dosage is supported by our data. Such a program allows for early intervention and may thereby prevent malnutrition, foster normal growth and weight gain, and possibly delay pulmonary function deterioration. With nutrition counseling and monitoring of dietary intake, we were able to achieve a mean energy intake comparable to that in enteral and parenteral alimentation programs. Therefore, nutrition counseling on a nonrestricted fat diet may be advantageous in postponing the use of invasive intervention methods that are not conducive to the normal life-style of adolescents and young adults.

This study was supported in part by grants from the Cystic Fibrosis Foundation, and the Division of Maternal and Child Health Training Grant MCJ001069, US Department of Health and Human Services, Rockville, Md.

References

1. Kraemer R, Rudeberg A, Hadorn B, Rossi E. Relative underweight in cystic fibrosis and its prognostic value. *Acta Paediatr Scand.* 1978;67:33-37.

2. Gaskin K, Gurwitz D, Durie P, Corey M, Levison H, Forstner G. Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. *J Pediatr.* 1982;100:857-862.

3. Gurwitz D, Corey M, Francis PWJ, Crozier D, Levison H. Perspectives in cystic fibrosis. *Pediatr Clin North Am.* 1979;26:603-615.

4. Pencharz P, Hill R, Archibald E, Levy L, Newth C. Energy needs and nutritional rehabilitation in undernourished adolescents and young adult patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 1984;3(suppl 1):147-153.

5. Reardon MC, Hammond KB, Accurso FJ, et al. Nutritional deficits exist before 2 months of age in some infants with cystic fibrosis identified by screening test. *J Pediatr.* 1984;105:271-274.

6. Levy LD, Durie PR, Pencharz PB, Corey ML. Effects of long-term nutritional rehabilitation on body composition and clinical status in malnourished children and adolescents with cystic fibrosis. *J Pediatr.* 1985;107:225-230.

7. Chase HP, Long MA, Lavin MH. Cystic fibrosis and malnutrition. *J Pediatr.* 1979;95:337-347.

8. Yassa JG, Prosser R, Dodge JA. Effects of an artificial diet on growth of patients with cystic fibrosis. *Arch Dis Child.* 1978;53:777-783.

9. Bertrand JM, Morin CL, Lasalle R, Patrick J, Coates A. Short-term clinical, nutritional and functional effects of continuous elemental enteral alimentation in children with cystic fibrosis. *J Pediatr.* 1984;104:41-46.

10. Shepherd R, Cooksley WGE, Cooke WDD. Improved growth and clinical, nutritional, and respiratory changes in response to nutritional therapy in cystic fibrosis. *J Pediatr.* 1980;97:351-357.

11. Mansell AL, Andersen JC, Muttart CR, et al. Short-term pulmonary effects of total parenteral nutrition in children with cystic fibrosis. *J Pediatr.* 1984;104:700-705.

12. National Research Council, Committee on Dietary Allowances. *Recommended Dietary Allowances.* 9th ed. Washington, DC: National Academy of Sciences; 1980.

13. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychological Rev.* 1977;84:191-215.

14. Hubbard VS, Mangrum PJ. Energy intake and nutrition counseling in cystic fibrosis. *J Am Diet Assoc.* 1982;80:127-131.

15. Block G. A review of validations of dietary assessment methods. *Am J Epidemiol.* 1984;115:492-505.

16. Adams CF. *Nutritive Value of American Foods in Common Units.* Washington, DC: US Dept of Agriculture; 1975. Handbook No. 456.

17. Cystic Fibrosis Foundation. *Patient Registry. Height and Weight of Cystic Fibrosis Patients.* Rockville, Md: Affiliated US Centers; 1985.

18. Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF. *NCHS Growth Curves for Children Birth-18 Years: United States.* Hyattsville, Md: National Center for Health Statistics; 1977. US Dept of Health, Education, and Welfare publication PHS 78-1650.

19. Abraham S. *Weight and Height of Adults 18-74 Years of Age: United States, 1971-1974.* Hyattsville, Md: National Center for Health Statistics, 1979. US Dept of Health, Education, and Welfare publication PHS 79-1659.

20. Berry HK, Kellog FW, Hunt MN, Ingberg RL, Richter L, Gutjahr C. Dietary supplement and nutrition in children with cystic fibrosis. *AJDC.*

1975;129:165-171.
21. Taussig LM. Standardization of lung function testing in children: Proceedings and Recommendations of the GAP Conference Committee: Cystic Fibrosis Foundation. *J Pediatr.* 1980; 97:668-676.
22. Weng TR, Levison H. Standards of pulmonary function in children. *Am Rev Respir Dis.* 1969;99:879-894.
23. Featherby EA, Weng TR, Crozier AD, Reilly AD, Levison H. Dynamic and static lung volumes, blood gas tension, and diffusing capacity in patients with cystic fibrosis. *Am Rev Respir Dis.* 1970;102;737-749.
24. Corey M, Levison H, Crozier D. Five- to seven-year course of pulmonary function in cystic fibrosis. *Am Rev Respir Dis.* 1976;114:1085-1092.
25. Cronk CE, Roche AF. Race and sex-specific reference data for triceps and subscapular skinfolds and weight/stature. *Am J Clin Nutr.* 1982;35: 347-354.
26. Rao KV, Singh D. An evaluation of the relationship between nutritional status and anthropometric measurements. *Am J Clin Nutr.* 1970;23: 83-93.
27. Winer BJ. *Statistical Principles in Experimental Design.* New York, NY: McGraw-Hill International Book Co; 1962.
28. Fleis JL. *The Design and Analysis of Clinical Experiments.* New York, NY: John Wiley & Sons; 1986:233.
29. Wilkinson L. *Systat: The System for Statistics.* Evanston, Ill: Systat Inc; 1988.
30. O'Loughlin E, Forbes D, Parsons H, Scott B, Cooper D, Gall G. Nutritional rehabilitation of malnourished patients with cystic fibrosis. *Am J Clin Nutr.* 1986;43:732-737.
31. Shepherd RW, Holt TL, Thomas BJ, et al. Nutritional rehabilitation in cystic fibrosis: controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease. *J Pediatr.* 1986;109:788-794.
32. Parsons HG, Beaudry P, Dumas A, Pencharz PB. Energy needs and growth in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr.* 1983;2:44-49.
33. Braun SR, Dixon RM, Keim NL, Andereff A, Shrago ES. Predictive clinical value of nutritional assessment factors in COPD. *Chest.* 1984;85:353-357.
34. Wilson DO, Rogers RM, Sanders MH, Pennock BE, Reilly JJ. Nutritional intervention in malnourished patients with emphysema. *Am Rev Respir Dis.* 1986;134:672-677.

Book Review

Pediatric Medicine, edited by Mary Ellen Avery and Lewis R. First, 1440 pp, with illus, $79.95, Baltimore, Md, Williams & Wilkins, 1988.

We guess that while gazing pensively out of the window of her third-floor, corner office overlooking Longwood Avenue, Dr Avery said to Dr First, "What this country needs is a good 5-lb pediatric text!" (Hoekelman's *Primary Pediatric Care,* 1987, 8 lb 6 oz; Rudolf's *Pediatrics,* 18th ed, 1986, 6 lb 7 oz; Nelson's *Textbook of Pediatrics,* 13th ed, 1987, 6 lb 14 oz.) The result of their labors is *Pediatric Medicine* (5 lb 7 oz), dedicated to the medical house staff of the Children's Hospital, Boston, Mass, whose observations and questions were the stimulus for this book.

The text is organized by organ system but also includes sections on well-child care, behavioral pediatrics, nutrition, oncology, genetics, rheumatology, childhood injuries, and toxicology. Each chapter is subdivided into "Definition," "Basic Science" (which includes material similar to that of the pathophysiology sections of other texts), "Epidemiology," "Natural History," "Diagnosis," "Treatment," "Prognosis," and "Prevention."

Major innovations in some chapters are subheadings devoted to "New Developments" and "Controversies," which highlight current dilemmas and sometimes outline explicitly the authors' approach. A welcome diversion is provided by the inclusion of case illustrations set in a different typeface and outlined in a box. These are consistently well written, informative, and thought provoking.

The book is handsome; the print is large and easy to read. The subheadings, set in bold type, are easily scanned. Graphs, illustrations, tables, and photographs are clear, pertinent, and plentiful. References, which include 1988 citations, are listed alphabetically at the end of the chapters, a less-convenient location than immediately after each topic. For example, the listing at the end of the 37–page chapter "Bacteria" includes over 150 references spanning topics from actinomycosis to *Yersinia pestis.* The index is comprehensive.

We attempted to compare this book systematically and objectively to three physically weightier, commonly used general pediatric texts. We each reviewed 30 common and uncommon conditions in each text. We could not reach a consensus. No one text seemed consistently superior. We learned that reviewing texts is very subjective: a discussion one of us regarded as superficial, the other might view as concise. There is much variation among chapters in multiauthored texts. In *Pediatric Medicine,* the style of the writing, clarity of thought, and presentation vary greatly among sections.

This text is written from the perspective of a referral center and seems to be aimed at the pediatric house officer. It often states unabashedly (albeit in the controversy sections) how "we do it" at The Children's Hospital. Whether this is welcome advice based on experience and reason or rather parochial empiricism probably depends more on the readers' than the authors' perspective. While it is not an encyclopedic text, neither is it superficial. It is a nourishing and digestible meat-and-potatoes (or perhaps baked beans) text, not a seven-course meal. *Pediatric Medicine* is a very useful starting reference but is not the ultimate pediatric text.

Jeffrey A. Wright, MD
Edgar K. Marcuse, MD, MPH
Department of Pediatrics
University of Washington
School of Medicine
Children's Hospital and
Medical Center
PO Box C5371
Seattle, WA 98105

THE BEST WAY TO COMBAT INFECTIOUS DISEASE IS TO SEE RED

Changes occur rapidly in the field of infectious diseases. The 1988 Report of the Committee on Infectious Diseases, commonly called the Red Book, offers important new information on a number of topics, including:

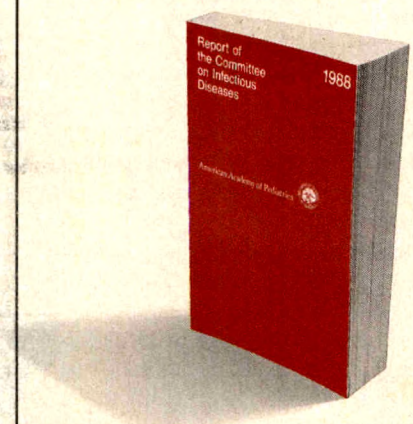
- Isolation precautions for hospitalized children
- Current guidelines on AIDS and HIV infections
- Children in day care
- New recommendations for hepatitis B
- Additional recommendations for pertussis
- New chapters on a variety of infectious diseases

The Red Book, published by the American Academy of Pediatrics, is one of the most respected pediatric reference manuals on infectious disease. It features 566 pages of infectious disease summaries, complete listings of reportable diseases, and state-by-state immunization laws, all efficiently organized.

The Red Book is just $25 for AAP members* and $30 for nonmembers. Hardbound copies are available for just $35 to members and $40 for nonmembers. Also available are reports of the task forces on pertussis and meningitis.

To get your copy of the Red Book, just call us toll free at 800/433-9016 (IL, 800/421-0589) to charge your order, or use the coupon.

*A complimentary copy has already been sent to all members of the Academy.



THE 1988 RED BOOK.

American Academy of Pediatrics

American Academy of Pediatrics
Publications Dept.
141 Northwest Point Blvd., P.O. Box 927
Elk Grove Village, IL 60009-0927

Please send me _____ copies of the Red Book ($25 for AAP members*, $30 for nonmembers. Hardbound edition is just $35 and $40, respectively. 1988, 566 pgs. ISBN 0-910761-20-5).

Also send _____ copies of the pertussis report ($6 for members, $25 for nonmembers) and _____ copies of the meningitis report ($6 for members, $15 for nonmembers).

Subtotal	_____
Handling charge per order	$3.50
Shipping (if applicable)	_____
TOTAL	_____

For every Red Book/pertussis report combination purchased, we'll include a meningitis report at no cost.

☐ Enclosed is my check/money order payable to the American Academy of Pediatrics. No shipping charges for prepaid, non-credit card orders.

For charge orders, complete the following or call toll free 800/433-9016 (IL, 800/421-0589). Shipping charges will be added to credit card orders.
Please charge my ☐ VISA ☐ MasterCard

_____

Exp. date _____

MC only, 4-digit # above bank name

_____

Please print:

Name _____

Address _____

City _____

State _____ Zip _____

Phone(_____) _____

AAP member? _____ yes _____ no

ID number _____

_____

Signature

Allow 2-3 weeks for UPS delivery

All AAP members are sent one complimentary copy of the Red Book. Use this form to order additional copies and individual reports.

Special Contribution

Adolescent Health

Synopsis of a Conference

Elizabeth Brown, MD, William R. Hendee, PhD (*Editors*)

• Adolescence can be subdivided into three interrelated components: biological, psychological, and sociocultural. Although the biological and psychological development of adolescents are largely generic processes, the social and cultural aspects strongly influence how these two processes are experienced. The plenary sessions of the First Annual American Medical Association Congress on Adolescent Health focused on the sociocultural factors that are currently influencing the adolescent experience. The lack of adult mentors in the job market, at home, and at school have left adolescents with minimal opportunities to interact with and learn from adults. Firm guidelines for responsible adult behavior have diminished, both through the subverting influence of television and the trend toward a value-neutral approach in education and preventive programs. Productive roles for adolescents have also dwindled; adolescents are primarily regarded as consumers. Physicians can help address these sociocultural issues by being a receptive and concerned adult to adolescents and to probe beyond simple presenting medical complaints to identify underlying development problems.

(*AJDC*. 1989;143:466-470)

Images of troubled adolescents pervade every socioeconomic stratum, from inner-city ghettos with teenage gangs to suburbia with teenagers listlessly roaming sprawling shopping malls. The risks of substance abuse, teen pregnancy, and emotional disorders threaten all children on their way to adulthood. Although most children succeed in this transition, many succumb to school failure, drug abuse, teen parenthood, crime, or delinquency.

Adolescence has always involved trial, experimentation, and a certain amount of risk. However, many of the risks that adolescents encounter today (eg, drug use and high-speed vehicles) have little counterpart in the adolescent experimentation of yesteryear. More than ever, adolescents need guidance, encouragement, and, frequently, intervention in charting their course toward adulthood.

The First Annual American Medical Associatin National Congress on Adolescent Health entitled "Charting a Course Through Turbulent Times" was convened May 12-14, 1988, to analyze the psychological, sociological, and economic issues influencing adolescent health and to highlight effective intervention programs addressing the issues of substance abuse, acquired immunodeficiency syndrome, injury, sexuality/pregnancy, emotional disorders, and victimization. The Congress attracted a diverse audience that included physicians, psychologists, school nurses and administrators, and representatives of several community organizations, such as 4-H and Girl Scouts.

In this synopsis, the plenary sessions of the Congress are summarized. A description of the 40 intervention programs highlighted at the Congress may be requested from the National Congress on Adolescent Health Workshops, Group on Science and Technology, American Medical Association, 535 N Dearborn St, Chicago, IL 60610.

Accepted for publication December 12, 1988.

From the American Medical Association, Chicago, Ill.

Reprint requests to the American Medical Association, 535 N Dearborn St, Chicago, IL 60610 (Dr Hendee).

History and Definition of Adolescence

William Braden, Chicago Sun-Times

Adolescence is the period of transition from childhood to adulthood. The transition can be subdivided into three interrelated components: biological, psychological, and sociocultural. The biological process pertains to the physical changes associated with puberty and young adulthood. Psychological development is a less visible process that involves concern about internal issues and how one relates to others. The sociocultural environment strongly affects how the biological and psychological processes are addressed by the adolescent. The combination of these three factors are unique for each adolescent; however, the evolving sociocultural environment has produced general trends in the adolescent experience. Examination of these trends yields an important perspective and insight into the current challenges of adolescence.

Before the Industrial Revolution and the emergence of the diversity of lifestyles and adult roles so prevalent today, the transition between childhood and adulthood was not acknowledged as a distinct period. That is, adolescence did not really exist in earlier times. In preindustrial times, when the population was centered mainly in rural areas, children were gradually absorbed into adult life by observing and then assuming adult tasks. With increasing age and stature, simple household tasks gave way to more demanding farm chores. The pathway to adulthood was followed by emulating visible role models provided by available adults.

Before the advent of child labor laws, children in cities were often abruptly forced into adult work roles at an early age. In England at the beginning of this century, for example, most children were instantly granted adult status and put to work when formal education ended at age 14 to 16 years. The transition from childhood to adulthood, ie, adolescence, could be as short as one weekend. This transition may have been harsh; however, the path to adulthood, although narrow and providing limited choices, was unambiguous and clear.

The Industrial Revolution required more skilled workers. This need, together with the growing urban population, the increasing numbers of working women, and the growth of labor unions, decreased the demand for child labor. Partially to protect adult jobs and partially in response to justifiable outrage over the working conditions of children, child labor laws were enacted that restricted employment to those over 16 years. At about the same time the arrival of massive numbers of immigrants with widely different backgrounds prompted the movement toward compulsory education for children between the ages of 6 and 16 years. School was a custodial as well as a learning institute for adolescents barred

from the workplace. The combination of child labor laws and compulsory education made adolescence a social reality.

The middle class, who could afford to invest more time and money in their children, began to recognize the importance of a good education as a ticket to upward mobility. This trend is still operative today. Although today's fast-paced technological society is more service oriented, it still places a high premium on education. The need for additional education has prolonged the period of adolescence. Psychologist Kenneth Keniston, PhD, suggests that the length of adolescence has been increasing about 1 year per decade, so that school now often extends into the middle 20s and beyond.[1]

As the concept of adolescence became a social reality in the late 1800s and early 1900s, psychologists and psychiatrists began to focus on its psychosocial dimensions. One of the first to enter this field was psychologist G. Stanley Hall who in 1904 described adolescence as a period of strong drama, storm, and stress. This basic theme was echoed by Sigmund Freud and his daughter Anna, who said that maintaining a steady equilibrium in adolescence is in itself abnormal, and that a tranquil adolescence was pathologic. The source of adolescent turmoil was attributed to the changing identity of adolescents as they struggled to establish an adult identity.[1]

From a cultural perspective, the broad range of opportunities and lifestyles initiated by the Industrial Revolution that are so prevalent today make the process of identity formation even more challenging. Adolescents are no longer mirror images of their parents, and the path to adulthood is ill-defined, abstract, and diverse. The psychologist Erik Erikson believed that adolescence should be a moratorium, a time of delay at the end of childhood "during which the individual through free role experimentation may find a niche in some section of society, a niche that is formally defined and yet seems to be uniquely made for him."[2]

As many observers focused on the pathologic behavior of adolescents, a popular concept emerged that portrayed adolescent turmoil and conflict as normal. Consequently, our culture has come to regard adolescents with apprehension and skepticism. Daniel Offer challenged that assumption by studying teenage boys longitudinally from 1963 until 1971 and found that most made a gradual and relatively painless transition from adolescence to adulthood. Offer concluded that dismissing adolescent turmoil as normal and unavoidable distracts much-needed attention from those teenagers who truly need professional help.[3] Furthermore, many well-adjusted teenagers are compromised by these negative stereotypes. Adolescence might better be approached from both a broad and an individual perspective. A broad perspective is needed to understand how our society and culture shape the adolescent world. At the same time, adolescents should be regarded as individuals and without negative stereotyping.

Adolescent Development and the Adolescent Process

Richard MacKenzie, MD, Childrens Hospital, Los Angeles, Calif

Adolescent development may be characterized by a progressive accumulation of experiences, which, in combination with physical and psychological development, promote increasing confidence, esteem, and wisdom and propel adolescents toward adulthood. The key to the transition to adulthood is the concept of choice; the ability to choose, to be exposed to and weigh options, is the foundation for developing adult responsibilities. Adolescents face many choices (few of them entirely risk free) that can propel them toward maturity, or arrest and even reverse progress. For example, as the concrete egocentric thinking typical of early adolescence is transformed into an ability to think abstractly, adolescents become capable of looking critically at the values and ethics embodied in adult society. Outright rejection of these values may produce adolescent alienation and a retreat into an isolated adolescent subculture, the only source of status and satisfaction perceived by the adolescent.

Many adolescents are physically capable of doing adult work. Yet their entry into the job market is largely denied until age 16 years, and then is confined primarily to service jobs at low pay and with little personal satisfaction. In response to this developmental crisis, some adolescents choose to join a subculture, such as a gang or drug culture. In this sense, the behaviors of adolescents and the choices they make are motivated by the adolescent developmental process itself. To the adolescent these choices are solutions to the perceived developmental crises of adolescence. Unfortunately, adults may perceive these choices as problem behaviors in themselves instead of symptoms of deeper underlying problems.

While the developmental crises of adolescence may be generic, solutions vary from adolescent to adolescent. Young people need to learn that developmental problems are part of adolescence, that they have options, and that aberrant behavior is not an effective solution. Unawareness of options or a feeling of impotence leaves adolescents in a vulnerable position.

Impoverished personal resources and support systems and blindness to options can force an individual into behaviors that not only have adverse health consequences but can also threaten pyschosocial development. Trust, security, and self-esteem are essential ingredients to development of a sense of identity and maturation to responsible independent functioning. Adolescents well integrated into adult society are more apt to use normative and acceptable behaviors to accomplish goals, while those who do not perceive these options, or who lack the personal resources or family support to pursue them, may resort to high-risk behaviors to achieve the same goals.

This perspective has important implications for how we view the risk-taking behavior of adolescents. When considering the problems adolescents face, it is easy to focus on adolescents themselves as the root of the problem. This "blame the victim" simplistic approach looks at troubled adolescents and their behaviors as the problem, instead of as symptoms related to the changes, and thus risks, that all adolescents experience. It is easy to label the teenager involved in drug abuse, irresponsible sexual activity, or reckless driving as perverse or deviant, when in reality these behaviors are a functional and purposeful response to adverse cultural factors experienced by the adolescent. Emphasis should not be placed on the risk-taking behavior itself, but rather should be focused on the purpose behind the behavior. While

some risk-taking behaviors may be pathogenic, they are not necessarily inherently pathologic.

This concept of adolescent development offers a clear challenge to physicians to better appreciate the complexity of issues and motivations underlying seemingly straightforward physical complaints. The lead point into many of those psychological maturational issues is often a physical complaint that is directly or indirectly related to risky behaviors. Gaining access to the underlying developmental issues can facilitate recognition of these behaviors and expedite intervention. Physicians and other health professionals should not be seduced into dealing only with the lead point. History taking should be wide-ranging and not focused solely on the physical complaint and a single diagnosis. Instead the physical complaint should be used as merely a starting point to explore a broad range of issues.

Physicians and other concerned adults must be willing to ask the appropriate questions. Many of these questions are sensitive, involving drug abuse, sexual activity, and life-styles or eating habits related to anorexia and bulimia. Judith Bensinger, MD, feels that these questions must be asked early, for example, in the routine office visit, even if the physical examination findings are completely normal. In this manner, adolescent problems can be recognized and confronted early, when they represent conquerable hurdles and not impenetrable brick walls.

However, it is not enough simply to ask the questions. Physicians must also be prepared to intervene when necessary and to match the intervention with the needs of the adolescent. In both a hospital setting and the physician's office, a multidisciplinary approach may be required. The primary level of adolescent health care involves a fixed physical complaint that may arise out of a natural disease process. A sore throat, for example, requires only the medical skills of the physician. With further exploration, however, it may become apparent that an adolescent's problems extend beyond the boundaries not only of an individual physician's expertise but also of medicine. Physicians should be prepared to enlist the assistance of a multidisciplinary team. A homeless adolescent involved in street prostitution or drug abuse is in need of tertiary care, not in the strict medical sense but in the broader sociocultural context. Psychologists, social workers, school officials, and the patient's family can be recruited to interact within the broader cultural context surrounding the patient.

Problems of Adolescent Rolelessness in Modern Society

Elena O. Nightingale, MD, PhD, Carnegie Corporation of New York, NY; William R. Hendee, PhD, American Medical Association; Joe Sanders, MD, American Academy of Pediatrics, Elk Grove Village, Ill

According to Erik Erikson, adolescence is a moratorium during which time the adolescent may explore and experiment with adult roles.[2] During this period adolescents need to find a role that promotes identity formation and provides a feeling of self-worth. This role must be valued by adolescents, while at the same time giving the adolescent an opportunity to interact with adults and to experience and experiment with adult responsibilities. Adult society should supply roles that welcome adolescents as contributing citizens and provide positive evidence that the transition to adulthood is a worthwhile and desired goal.

Adolescents today face an age-segregated society that offers little opportunity for interaction with adults. The changing economy provides few self-supporting jobs for young people. Adolescents frequently perceive a hostile and deeply divided adult society. These factors have eliminated many niches for adolescents and made it increasingly difficult for adolescents to safely experiment with adult roles and expectations.

One of the most visible signs of a successful transition to adulthood is the acquisition of a meaningful job. The job market for adolescents used to offer a direct path to adulthood. In an agrarian economy, adolescents gradually assumed adult work roles by observing parents. While these tasks may not have been salaried, they did provide direct interaction with adults, and adolescents felt they were contributing to the economic success of the family and community.

Today's job market is diffuse and abstract. Adolescents may never see firsthand what their parents do during the day. Even at home, adolescents often have little contact with their parents. One study showed that adolescents typically spend less than 5% of their time with parents.[4] Manufacturing jobs used to be a typical entry point of adolescents into the job market. High school graduates and even dropouts could be assured of a well-paying job capable of supporting a family. Manufacturing jobs also offered the protection of the union and employers were willing to invest in and train young workers.

The transition of the American economy from industry and manufacturing to service and retail has radically changed the job market for adolescents. The increasing importance of education has placed a significant barrier between school and the workplace and has restricted the job opportunities for adolescents. Service and retail jobs tend to offer low pay with irregular hours and limited opportunities for advancement.

Teenagers are additionally disadvantaged by the ambivalent way in which adults view adolescents. Many employers feel that adolescents are irresponsible, poor workers, a poor investment, and easily replaced. The result is that many companies resist putting young workers on a promotional track for a meaningful job until they are at least in their middle 20s. A high school dropout may have to wait ten or more years before receiving any real chance in the adult job market. By that time, the drive to succeed may have disappeared. Minimum-wage jobs will not support an intact family of three above the poverty level. This is a tremendous burden for young parents trying to make a commitment to traditional family life. Although they may have adult responsibilities they are in effect shut out of adult work roles.

For adolescents living in areas of concentrated poverty, the problem is even more acute. Many of these youngsters have little or no contact with adults who are supporting a family with a legitimate job. For them, the most accessible role models are members of gangs or persons involved in the drug subculture. It is hard to convince an adolescent drug dealer who is making $2000 a week to accept a minimum-wage job as a busboy,

or to convince a young prostitute making $1000 a week that she would be better off working as a waitress at minimum wage.

Many of the more affluent adolescents do obtain part-time jobs not to support themselves but only to earn extra pocket money. A typical part-time job might be working in a fast-food restaurant. While the low wage of these jobs might be less important in this situation, the jobs provide little opportunity to experiment with an "adult" type work role. In part-time jobs in the service and retail industries, adolescents work most commonly alongside other adolescents. There are few opportunities for adolescents to interact with an interested adult mentor. Furthermore, income is used for pleasure, leisure, and the trappings of the adolescent peer culture. These relatively affluent teenagers are usually not required to contribute to the family's income and thus get a distorted view of the real significance of a job.

The most identifiable role for these adolescents is as consumers, members of an enforced leisure class. In fact, adolescents spend up to 40% of their time in leisure activities, a role that demands very little from teenagers. This role is not lost on advertisers who aggressively market their products to teenagers, taking advantage of the shifting tastes of the adolescent peer culture.

From the adolescent viewpoint, the definition of an adult is ambiguous and frequently negative. Our culture grants adult status to various activities at various times. For example, legal driving ages range from 16 to 18 years, and in most states the voting age is lower than that for drinking. Adolescents recognize that adults have had limited success in addressing many of the persistent problems of our society, such as poverty, threat of war, dwindling natural resources, and environmental pollution. Unethical behavior of government officials is a frequent and highly reported occurrence, and there are few adult heroes who serve as positive role models. At the same time that adolescents are examining the failures of adults, they see limited opportunities for their generation to contribute in any meaningful way. The situation is aggravated by adults who tend to dismiss adolescents as immature and irresponsible persons who have no concept of the real world.

Community service programs have a great potential to bridge the gap between adolescence and adulthood. These programs can be as simple as linking adolescents with retired people. Interviews with middle school students who regularly visited a nursing home in inner-city New York revealed that the students were able to make friends with elders that they had previously viewed with intimidation and, not infrequently, hostility. The students worked hard and were liked by their elderly companions. Even doing simple tasks like bringing a snack to an immobilized person can create a feeling of self-worth and appreciation. Community service programs can also offer opportunities to succeed at nonacademic tasks. Optimal programs would be styled as apprenticeships where participants have opportunities for systematic examination of their experience and feedback from an adult mentor. Some business, religious, and youth organizations have provided these types of mentoring activities. There are a number of social institutions that could provide social supports and human anchors for adolescents who are adrift. Physicians could serve as catalysts in their communities to orient these institutions to the needs of adolescents.

Adolescents who are shut out of the adult world can hardly be expected to make an easy transition to adulthood. There has been considerable discussion about what can be done about adolescents and for adolescents. Now, responsible adults should concentrate on what they can do with adolescents, spending time with them, interacting with them, and making them feel welcome in adult society.

Family and Community: A Reciprocal Relationship

George D. Comerci, MD, University of Arizona, Tucson;
Robert H. DuRant, PhD, Medical College of Georgia, Augusta;
Judith Bensinger, MD, Private Practice, Highland Park, Ill

Adolescence is a psychosocial maturation process—the developmental continuum between childhood and adulthood during which dramatic physical, psychosocial, cognitive, and moral-ethical changes occur. Achievement of adult status and autonomy is not merely the physical and psychological separation of the adolescent from parents; it is also the establishment of a personal identity and the assumption of new roles and relationships within one's community. The sociocultural milieu strongly influences the degree to which adolescents are embraced and made to feel welcome by the adult members of a community. The family and community are the major components of this milieu, and the values they present strongly affect the integration of adolescents into adult society.

One way to view the relationship between adolescents and their sociocultural milieu is as a series of subtle, unwritten contracts. For example, parents, society, and the community grant freedom to adolescents in exchange for responsible behavior. Likewise, they provide economic and emotional support in exchange for a child's loyalty. In return, loyalty is offered by adolescents in exchange for commitment by parents and community. Several trends in our society, including the increasing number of working parents and single-parent households, an early emphasis on achievement, and an inconsistent adult society, have seriously compromised the abilities of adults to uphold their contracts with children.

For many young people, the full-time employment of both parents means growing up too fast. Children return after school to empty houses and prepare their own meals, wash their own clothes, do other household chores, and otherwise care for themselves. Autonomy and independence are thrust upon children at an early age, even though they may not be ready for them.

The problem is further aggravated by single-parent households, which are increasing due to the high number of divorces, separations, and extramarital pregnancies. Single parenthood adds to the economic burden of the family and forces many women into the workplace for the first time. Moreover, adults often feel that they must focus on themselves after a separation or divorce, to reorder their own lives and start over again. Frequently, adolescents are forced into a kind of role reversal and pseudomaturity in which they observe the parent participating in adolescentlike romances, courtships, and remarriages. This adolescentlike behavior of the adult can be interpreted as tacit approval for a

child's own precocious sexual experimentation. At a time when parents should be supporting and guiding adolescent children, the adolescent is asked to assume the adult role of counselor to the parent. Sometimes the attitude of the parent can be even more extreme, implying outright rejection. In these situations, the parent's contract of commitment is entirely negated.

Our upwardly mobile society has put an early emphasis on achievement. Children are expected to do well in school, not only for the sake of achievement alone, but also as a prerequisite for college and a future career. In fact, both parents may be working to ensure that their children can take advantage of the best schools and other enriching opportunities. These parents may have little time or energy left over to provide the necessary personal support for the child's expected achievement. For children who live in poverty, and an increasing number of them do, there is simply no economic support to sponsor and encourage achievement.

The contract of freedom in exchange for adolescent responsibility presumes that adolescents are aware of the definition of responsible behavior. Adolescents need rationally justified, stable, coherent adult values against which to test their own emerging moral guidelines. American society is reneging on this contract by failing to provide consistent guidelines for responsible moral behavior. For example, parents who use illicit drugs or who have multiple or illicit sexual relationships present confusing and inconsistent role models for their children.

The pervasive presence of television similarly presents a confusing world and makes it impossible to introduce children and adolescents into the adult world in a balanced and measured way. Television is an immediate window into the adult world and children can be exposed to as many forms of society as there are channels on their television sets. Explicit sexual references and sexual innuendo are present in all genres of television shows. Premarital and extramarital sex are rife, and often the illicit relationship is depicted as the most daring and rewarding. There are no secrets for adolescents; they have been exposed to everything through television.

Society at large has not actively participated in creating guidelines for responsible behavior. A trend in adolescent health care provision, education, and prevention programs has been toward a value-neutral approach. Beginning in the late 1960s, the focus of these programs turned toward individuality, freedom of choice, and fulfillment—so long as no harm was done to anyone. As a result, firm guidelines for responsible behavior were not integrated into these programs and negative sanctions for inappropriate behavior were weakened. For example, many preventive educational programs on adolescent sexuality and drug experimentation focus strictly on objective information, while remaining neutral on the larger issues of responsible ethical and moral behavior.

This value-neutral attitude may increase adolescent alienation by weakening parental authority and the disciplinary bond between parents and children. This value-neutral approach is currently undergoing reevaluation. Recently, health care professionals and developmental psychologists have recognized that a renewed interest in the moral values of everyday life and strong family attachment and supervision during adolescence will enhance the relationship between teenagers and their parents. There is an emerging consensus that successful negotiation of the adolescent transition lies not in asserting independence for the purpose of overcoming the dependency of childhood, but rather in establishing patterns of interdependence through family reorganization of responsibilities and personal relationships. Therefore, education and intervention programs must be developed with the cooperation and input from parents. However, in our pluralistic society it is important that the values imparted in a public program represent the consensus of the parents' values in each local community.

The dynamic physical and psychosocial development of adolescence make this period a time of both great vulnerability and great promise. If adolescents are to fulfill this promise, they must have the reassurance that they are part of a family and community that are stable, predictable, and friendly. They must feel encouraged rather than impeded in their efforts to attain rewarding adult goals in a caring and responsible society.

CONCLUSION

Pressing health issues facing adolescents, including substance abuse, teenage pregnancy, and violent behavior, have deep and complex roots that are related at least in part to current economic realities and the attitudes and values of our culture. If we approach the health issues of adolescents as problems of individual deviance, then the broader underlying social problems will remain undiagnosed and untreated, and only adolescents' symptoms will be treated.

Many of the underlying problems are related to an adult society that is separated from and sometimes frankly hostile to adolescents. To make the transition to adulthood, adolescents need to interact with adults in both abstract and concrete ways. Adults must become more consistent role models for adolescents, both as parents and as members of adult society. Adolescents need firm and consistent guidelines and a clearer definition of the path to adulthood. More concretely, adults should spend more time with adolescents. Adolescents need adult mentors who can provide active guidance and feedback as adolescents experiment with adult roles in school, in the workplace, and at home. Adults must provide a welcome mat for adolescents.

Physicians have opportunities to make a significant contribution to this process. They can take advantage of their natural position of community leadership to educate and encourage responsible behavior of adolescents and their parents. Physicians who have a long-term relationship with an adolescent can serve as an interested and concerned adult mentor. Physicians should also explore the underlying sociocultural environment of the adolescent and be prepared to enlist the support of a multidisciplinary team both from within and outside medicine whenever appropriate.

References

1. Braden W. *The Age of Aquarius, Technology and the Cultural Revolution*. New York, NY: Quadrangle Books; 1970.
2. Erikson E. *Identity, Youth and Crisis*. New York, NY: W. W. Norton & Co; 1968.
3. Offer D, Ostorov E, Howard K. *The Adolescent*. New York, NY: Basic Books Inc Publishers; 1987.
4. Csikszentmihalyi M, Larsen R. *Being Adolescent*. New York, NY: Basic Books Inc Publishers; 1984.

Determinants of School Performance in Children With Chronic Asthma

Linda B. Gutstadt, MEd; Jerry W. Gillette, MEd; David A. Mrazek, MD; Joleen T. Fukuhara; John F. LaBrecque, PhD; Robert C. Strunk, MD

• We have documented performance on standardized academic achievement tests for reading and mathematics in 99 children with moderately severe to severe chronic asthma. Academic performance and intelligence test scores indicated that, overall, the academic capabilities of the children with asthma were average to above average. A stepwise regression analysis was used to examine relationships between the dependent variables of reading and mathematics and the independent variables of socioeconomic status, school attendance, medical factors relating to asthma, age, and emotional and behavioral problems of the children. Factors that were associated significantly with low performance scores were low socioeconomic status, older age, history of continuous oral steroid use (prednisone or methyl prednisolone taken at least every other day for the year prior to evaluation), and presence of emotional and behavioral problems. School absenteeism, use of medical resources, oral steroid dosage, other medications used to treat asthma, and pulmonary functions were not associated with academic performance. Investigation of poor classroom performance of a child with chronic asthma should include investigation of the roles of socioeconomic status, oral steroid therapy, and emotional and behavioral problems.

(*AJDC*. 1989;143:471-475)

School-related problems are a frequent concern in pediatric practice.[1] One of the most important problems is frequent absenteeism. Children who are frequently or persistently absent from school are likely to drop out before graduation from high school.[2] These children are also likely to perform poorly in school.[2,3] Numerous studies have indicated that both physical and mental health problems of students and their family members contribute to frequent absenteeism.[4,5] Several investigators have even concluded that excessive absenteeism may be an indicator of social maladjustment or an early indicator of depression.[2,6]

Even though asthma is the most common chronic illness in childhood and accounts for more school absenteeism than any other chronic illness,[7] there have been very few studies of the relationships between asthma, absenteeism, and school performance. Several studies have demonstrated that children with asthma are absent from school significantly more often than are their nonasthmatic peers.[8-10] In one study, the rates of school absence correlated directly with maternal perception of the severity of the child's asthma, although the severity was not verified medically.[8] There have been even fewer studies of academic performance in children with asthma. In the most widely quoted study, approximately 40% of the parents interviewed indicated that their child had difficulty in school.[11] The two major problems were an increased number of absences and reading difficulties. However, information about school attendance, classroom performance, and the nature of the academic problems was obtained only through parent interviews. Actual records of attendance and grades were not obtained, and standardized testing was not administered to document academic performance.

The purpose of the present study was to document performance on standardized academic achievement tests in a group of children with chronic asthma. Since school performance can be influenced by multiple factors, a comprehensive understanding of the relationships between asthma and school performance should include examination of the relationships between academic performance, school attendance, and emotional and behavioral problems, as well as medical factors relating to asthma.

PATIENTS AND METHODS

Patients

The 99 patients (50 boys and 49 girls) included in this study were consecutive referrals for evaluation and rehabilitation of severe chronic asthma. They were between the ages of 9 and 17 years (mean age [±SD], 12.7±2.2 years). All 99 patients had a primary diagnosis of asthma according to the definition of the American Thoracic Society.[12] At the time of evaluation their asthma was stable; ie, they had not been hospitalized for status asthmaticus for several weeks and were at their best functioning level (this may have included daily asthma symptoms for some children). Grade placements ranged from second to 12th. The patients were admitted to the inpatient pediatric unit at the National Jewish Center for Immunology and Respiratory Medicine, Denver, Colo, for evaluation and rehabilitation of their asthma.

The medical variables describing each child's asthma are shown in Table 1. This information was extracted from the medical summary, the referring physician's report, and information obtained during evaluation of the patient in the hospital. Pulmonary function testing was performed according to standardized procedures.[13] The patients had moderately severe to severe asthma that had been present for many years (mean age at onset and evaluation was 2 and 12 years, respectively [Table 1]). Twenty percent of the patients had a history of respiratory failure and/or hypoxic seizures during asthma attacks (not idiopathic epilepsy). Fifty percent had been hospitalized for asthma at least once in the year prior to evaluation, and 55%

Accepted for publication December 31, 1988.

From the Departments of Education and Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, and the Departments of Pediatrics and Psychiatry, the University of Colorado School of Medicine, Denver. Dr Strunk is now with the Department of Pediatrics, Washington University School of Medicine, St Louis, Mo.

Reprint requests to Department of Pediatrics, Washington University School of Medicine, 400 S Kingshighway Blvd, St Louis, MO 63110 (Dr Strunk).

Table 1.—Medical and Psychological Characteristics of the 99 Patients

	Median (Range)
History	
Age at onset of asthma, y	2.0 (0.1-14.0)
Medical utilization in year prior to evaluation*	
Hospitalizations	1 (0-15)
Hospital days	6 (0-73)
Office visits for acute asthma	5 (0-36)
Emergency department visits	1 (0-36)
Medical observations	
Oral steroid dosage at time of evaluation (mg in daily prednisone equivalent)	7.5 (0-250)
	No. of Patients
History of respiratory failure requiring ventilation	18
History of seizures (hypoxic) during asthma attacks	15
Oral steroid use in year prior to evaluation	
None or episodic only	46
Continuous, daily or every other day	55
Exacerbation of disease in year prior to evaluation	60
Medications prescribed by referring physician at time of evaluation	
Theophylline	94
β-Agonists	
Oral	53
Inhaled	89
Cromolyn	32
Steroids	
Oral	68
Inhaled	25
Troleandomycin	2
Pulmonary function testing	
Forced expiratory volume in 1 s less than 80% of predicted	16
Thoracic gas volume greater than 120% of predicted	55
Socioeconomic status	
Major business and professional	13
Medium business, minor professional, technical	50
Skilled craftsman, clerical, sales workers	20
Machine operators, semiskilled workers	12
Unskilled laborers, menial service workers	4
	Median (Range)
Psychological observations	
Child Behavior Checklist (total score)†	61 (40-89)

*Medical utilization was determined by calling all the medical facilities used the year prior to evaluation and confirming numbers of hospitalizations, days in hospital, emergency department visits, and physician office visits for acute asthma.

†Child Behavior Checklist scores greater than 64 indicate significant emotional and behavioral problems.[19] Using this cutoff point, mothers identified 36% of the children as having emotional and behavioral problems.

Table 2.—Evaluations Performed

Academic testing*
For students 9 to 12 years of age
Woodcock Reading Mastery Tests[14]
Key Math Diagnostic Arithmetic Test[15]
For students 13 to 17 years of age
Woodcock - Johnson PsychoEducational Battery (part II, tests of achievement)[16]
Intelligence testing
Slosson Intelligence Test (expressed as deviation intelligence quotient scores)[18]
Psychological assessment
Child Behavior Checklist (overall assessment of emotional and behavioral problems [only the total score was used])[19]

*Scores were expressed as standardized *T* scores, which allow comparison of academic performance in children over a wide age range.

had used an oral steroid preparation (either prednisone or methyl prednisolone) continuously during the year. Pulmonary function test results at the time of evaluation were abnormal, primarily for increased lung volumes. The relatively normal flows reflected the stable status on entry into evaluation and the extensive use of medicines, including oral steroid therapy in 68% of patients (median dose for all patients was equivalent to 7.5 mg of prednisone per day).

Ninety-five percent of the children had attended public schools before evaluation. Ninety percent of children were white and 7% were black; the remaining 3% were of different races.

Academic Testing

Standardized tests of academic performance were administered to the children.[14-16] The test given was selected based on each child's age (Table 2). The scores of these tests were expressed using *T* scores, which are standardized scores based on a distribution of test scores in a normal population.[17] *T* scores have a mean of 50 and an SD of 10.

Intelligence Testing

The Slosson Intelligence Test[18] was chosen as the measure of intelligence because of ease of administration to large numbers of children. Results of Slossen testing correlate highly ($r = .95$) with results of the Stanford-Binet Test, a more complete measure of IQ.[18] The scores were expressed as deviation IQ scores (mean = 100; 1 SD = 15).[18]

Attendance Records

Educational records indicating school attendance for the semester prior to evaluation were obtained by contacting each child's home school. When available on the records, grades were categorized as average to above average (C or above, numerical grade ≥70, and pass or equivalent) or below average (homebound children and drop-outs were included here).

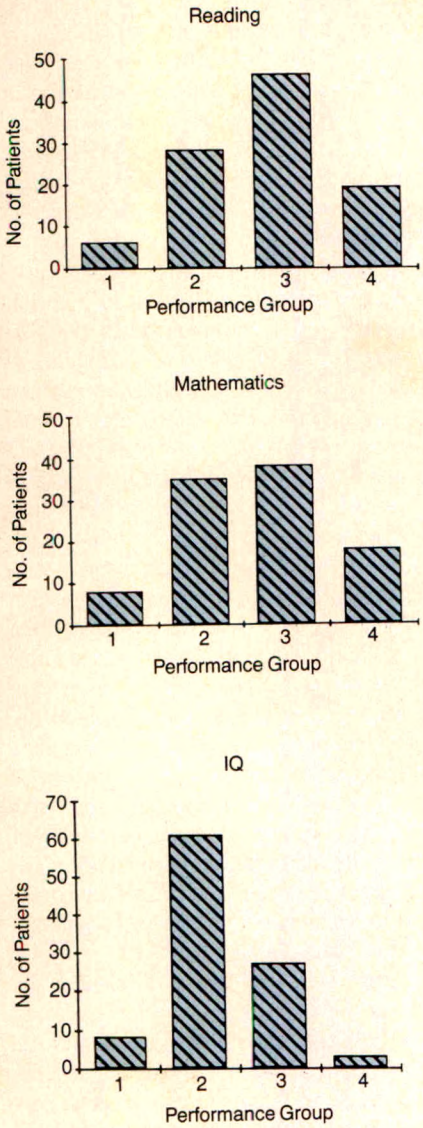
Psychological Variables

Emotional and behavioral problems in the children were assessed using the standardized Child Behavior Checklist (CBCL),[19] which was completed by the mothers or primary caretakers. This is a checklist of common childhood behavior difficulties. The total score gives an overall measure of emotional and behavioral problems. Each family's socioeconomic status (SES) was determined using the Hollingshead Scale.[20]

Testing Procedures

Parents gave consent for participation of their child in the study. The study design and consent form were approved by the National Jewish Institutional Review Board, Denver, Colo.

Academic performance and intelligence tests required two individual 1-hour sessions conducted by a single educator (L.B.G.). The tests were administered during the first 2 weeks of evaluation, so that the results would reflect academic performance in the home school and not be influenced by the schooling they would receive at the National Jewish Center. Pulmonary function testing was performed within the first 24 hours of evaluation. Data for determination of SES were collected during intake by the nurses and social workers. The primary clinical social worker responsible for evaluation of the family assessed the functioning of the child and requested that the mother complete the CBCL. The data were collected indepen-



Frequency distributions of academic test performance, expressed as standardized *T* scores, and IQ scores for the 99 patients. For normal populations, *T* scores have a mean of 50 and an SD of 10; IQ scores have a mean of 100 and an SD of 15. Performance groups for reading and mathematics are as follows: 1, less than 40; 2, 40 to 50; 3, 51 to 60; and 4, greater than 60. Performance groups for IQ: 1, 73 to 84; 2, 85 to 115; 3, 116 to 130; and 4, greater than 130. Mean (range) for reading, 52.5 (27 to 73); for mathematics, 52.4 (29 to 73).

dently by the services. None of the services had knowledge of the results from the other services.

One hundred consecutive referrals were eligible for the study. One patient was not included because his term of evaluation occurred during the winter vacation of the National Jewish Center's school. Data collection on the 99 patients was complete except for the CBCL (only 84 patients were assessed with the CBCL). The most common reasons for incomplete CBCL data were the mother or the primary caretaker not accompanying the child and a lack of compliance by the mother or caretaker to complete the CBCL. The 14 patients not included because of missing CBCLs were not different from the remaining children with regard to academic performance, severity of asthma, or psychological adaptation as assessed by the clinical social workers.

Statistical Analysis

For these analyses, the two achievement tests (reading and mathematics) were considered as dependent variables. Potential adverse effects of severity of disease and psychological functioning on the achievement scores were examined. Each of the dependent variables was examined separately as a function of the remaining variables using a stepwise regression analysis.[21] Characteristics of the child and the asthma (independent variables) were added to the analysis one at a time to determine the effect of each characteristic on the degree of variance observed in the dependent variable. When a characteristic was related significantly to a dependent variable, the characteristic was retained in the analysis. In this way, subsequent independent variables added to the analysis were judged as significant only if the contribution to the variance was significant over and above the contribution of the previous variables.

RESULTS
Academic Performance, IQ Scores, and Absenteeism

Scores on the standardized tests for academic performance were average or slightly above average, with mean *T* scores of 52.5 and 52.4 for reading and mathematics, respectively (*T* scores are standardized so that the mean in a normal population equals 50[17]) (Figure). The IQ scores were also average to above average (Figure) and correlated with the mathematics and reading scores ($r^2 = .55$ and $r^2 = .38$, respectively). Grades from the home school for the semester prior to evaluation were also consistent with average functioning, with 80% of the patients on whom information could be obtained receiving at least average grades in both reading and mathematics. Grades were not used in subsequent analyses because they were unavailable from the home school in a large percentage of the children (17% for mathematics and 25% for reading). In addition, the scoring systems used by the home school were highly variable, ranging from giving a smile for a good job, to a simple pass-fail, to traditional grade point averages.

School absenteeism in the semester prior to evaluation ranged from 0% to 94% of possible days, with a median of 20 days. Most missed days of school were not spent in the hospital (the median for days in the hospital was 6 in the preceding year [Table 1], compared with 20 missed days of school in the preceding semester, or approximately 40 missed days of school per year). Assistance with school work during these absences would have been provided primarily by parents, as homebound education by schools is provided only for absences of greater than 1 week. School absenteeism was not correlated with any of the variables listed in Table 1, including history, medical observations, socioeconomic status, and psychological observations. None of the children exhibited signs of school phobia while in the National Jewish Center school.

Comparison of Academic Performance With Medical and Psychological Variables

Next we sought to determine the impact of asthma and its treatment on academic performance. This was done using a stepwise regression analysis in which the relevant variables were added one at a time and the significance of each variable was then determined. Since the independent variables are related to each other, the order in which variables are entered into the analysis affects the judgment of their relative importance. The SES and absences were entered first, because these variables have been related to academic performance in other settings. The medical variables were added next, followed by the frequency of emotional and behavioral problems (CBCL).

The results indicated that SES was significantly correlated with academic performance (low SES was associated with low performance) (Table 3). The association between SES and academic performance has also been noted in children without chronic illness.[22] Interestingly, the percentage of days that a child was absent from school did not correlate with performance.

Table 3.—Contributions of Medical and Psychological Variables to the Variance in Academic Test Scores*

Variable Entered	Cumulative r^2	
	Mathematics	Reading
Socioeconomic status	.09	.18
History of oral steroid use in preceding year	.14	.22
Age at time of testing	.26	.27
Child Behavior Checklist (total score)	.33	.33

*Results of multivariate analyses. Entry of these independent variables was significant at the least at the .05 level.

The impact of the variables defining asthma and its treatment was considered next. Most variables did not correlate with performance: utilization of medical resources in the year prior to evaluation, history of either respiratory failure or hypoxic seizures, medications being taken at the time of evaluation (including the amount of steroid medication [prednisone or methyl prednisolone]), and pulmonary functions. Only history of steroid use in the preceding year entered the regression analysis at a significant level (use of oral steroids, either prednisone or methyl prednisolone, taken continuously at least every other day for the year prior to evaluation, was associated with low performance) (Table 3).

Next we considered the impact of length of the disease on academic performance, hypothesizing that the longer the disease had been present the more impact the asthma might have on performance. Neither age at onset nor length of disease alone had a significant impact. However, when age at onset and length of disease were added together, they made a significant contribution to mathematical performance (earlier onset and longer duration of disease were associated with low performance, data not shown).

Since age at onset and length of disease together are essentially age, age was substituted for these two variables. In this case there were significant results for both mathematics and reading (older age was associated with low performance). Since different tests were administered to children who were younger and older than 12 years of age, mean scores were compared in the two age groups. The standard scores did not show any statistically significant differences between the two groups, suggesting that the effect of age observed in the stepwise regression analysis was not related to the different tests used.

The final variable involved the assessment of emotional and behavioral problems. The CBCL score improved the r^2 values in both areas of academic performance, ie, mathematics and reading (Table 3). In each case, poor functioning was associated with low performance. Together, all of the independent variables accounted for 33% of the variability of the dependent variables (ie, $r^2 = .33$) (Table 3).

COMMENT

This study demonstrates that performance on standardized academic tests in a group of children with moderately severe to severe asthma was average to above average, even though the children were absent from school one fifth of the days in the semester prior to the testing. The average to above average academic scores of the children in our study are distinctly different from the parent impressions reported by Freudenberg et al[11] that approximately 40% of children with asthma have problems in school, especially in the area of reading. Although the description of the medical problems in the sample reported by Freudenberg and colleagues was incomplete, it is likely that the asthma in our patients was much more severe. Thus, we expected to find more problems than had been previously reported. Other factors may have influenced the results; specifically, a high percentage of our patients had a high SES, and our patients had been referred to a national center for evaluation and rehabilitation of severe asthma. Both of these factors may reflect high motivation, which in turn could influence academic performance. Socioeconomic status is known to correlate with school performance.[22] While our findings may have been affected by the special nature of the population studied, they clearly indicate that patients with moderately severe to severe asthma can perform normally in standardized academic performance tests.

The lack of a correlation between academic performance and school absenteeism was surprising. It is possible that the average levels of intelligence of the children in this study allowed them to compensate for time missed from school. When considered along with the correlation between academic performance and emotional and behavioral problems, the lack of a correlation between performance and absences suggests that a child who misses a considerable amount of school because of asthma can maintain the expected academic performance if the underlying psychological adaptation is good. The hypothesis that psychological functioning may be important in determining the level of day-to-day functioning of children with chronic asthma in school is consistent with the findings that psychological adaptation of patients with asthma correlated with gross and fine motor coordination[23] and physical fitness.[24]

Results of analysis to determine the basis for the variability in test scores indicate that the severity of the asthma and the drugs used to treat the asthma had little or no impact on academic performance. Only a history of oral steroid use correlated significantly with performance. This finding is consistent with findings of other authors. Stump[25] has reported that children who were taking at least 20 mg of prednisone every other day for 2 weeks or longer had significantly lower scores in mathematics than did children who were receiving lower dosages or theophylline alone; there was no difference in mathematical scores between the days patients were and were not receiving steroids. Suess et al[26] demonstrated that oral steroid use was associated with deficits in memory, providing a possible mechanism for the relationship between steroid use and lower mathematical performance. The lack of a correlation between academic performance and dosage of steroid therapy (in this study) and the similarity in mathematical scores on the

days patients were and were not receiving steroids[25] suggest that the effect of steroids on the learning process is cumulative rather than short term. However, none of the studies indicate that oral steroid use plays a major role in determining school performance, especially over and above the impact of IQ and SES.

The emotional and behavioral problems of the patients, as determined by the standardized CBCL, were significantly correlated with academic performance (Table 3). By itself, the CBCL was significantly correlated with performance (mathematics, $r = -.39$ and $P = .0002$; reading, $r = -.29$ and $P = .007$). Since the CBCL may have achieved some of its impact because of correlations between it and SES or other variables, we added it last to the regression analysis. The CBCL still added a significant amount of information to the analysis when it was added after the variability due to SES, history of steroid use, and age had been considered (Table 3). The role of emotional and behavioral problems in determining performance in children with chronic illness requires further study.

Since school is such a major portion of a child's life, complete care of a child with asthma should include attempts to increase that child's academic performance to the highest level possible. Investigation of poor classroom performance in children with chronic asthma should include analysis of the roles of SES, oral steroid use, and emotional and behavioral problems in addition to consideration of the child's basic intelligence.

This investigation was supported in part by an Allergic Diseases Academic Award (K07-AI 00543) to Dr Strunk, a Research Scientists Development Award (K01-MH 00430) to Dr Mrazek, and a grant from the National Jewish Center for Immunology and Respiratory Medicine, Denver, Colo.

We would like to thank the staff of the Beaumont Learning Center at National Jewish Center for Immunology and Respiratory Medicine for their contributions and to Jane Watkins and Julie Hildebrandt for preparation of the manuscript.

References

1. Burnett RD, Bell LS. Projecting pediatric practice patterns: a survey by the American Academy of Pediatrics Committee on Manpower. *Pediatrics*. 1978;62(suppl):625-680.

2. Weitzman M, Klerman LV, Lamb G, Menary J, Alpert JJ. School absence: a problem for the pediatrician. *Pediatrics*. 1982;69:739-746.

3. O'Neil SL, Barysh N, Setear SJ. Determining school programming needs of special population groups: a study of asthmatic children. *J Sch Health*. 1985;55:237-239.

4. Rogers KD, Reese G. Health studies—presumably normal high school students. *AJDC*. 1965;109:9-27.

5. Frerichs AH. Relationship of elementary school absences to psychosomatic ailments. *J Sch Health*. 1969;39:92-95.

6. Boardman V, Byzanski S, Cottrell L. School absences, illness, and family competence. In: Kaplan BH, Cassel JC, eds: *Family Health: An Epidemiologic Approach*. Chapel Hill, NC: Institute for Research in Social Science, University of North Carolina; 1975:63.

7. American Academy of Pediatrics Committee on Children with Handicaps. The asthmatic child and his participation in sports and physical education. *Pediatrics*. 1970;45:150-151.

8. Parcel GS, Gilman SC, Nader PR, Bunce H. A comparison of absentee rates of elementary school children with asthma and non-asthmatic school mates. *Pediatrics*. 1979;64:878-881.

9. Mitchell RG, Dawson B. Educational and social characteristics of children with asthma. *Arch Dis Child*. 1973;48:467.

10. Creer TL, Yoches C. The modification of an inappropriate behavioral pattern in asthmatic children. *J Chronic Dis*. 1971;24:507.

11. Freudenberg N, Feldman CH, Clark NM, et al. The impact of bronchial asthma on school attendance and performance. *J Sch Health*. 1980;50:522.

12. American Thoracic Society. Definition and classification of chronic bronchitis, asthma and pulmonary emphysema: a statement of the American Thoracic Society. *Am Rev Respir Dis*. 1962;85:761-768.

13. Cherniak R. *Pulmonary Function Testing*. Philadelphia, Pa: WB Saunders Co; 1977.

14. Woodcock RW. *Woodcock Reading Mastery Tests*. Circle Pines, Minn: American Guidance Service; 1973.

15. Connolly A, Nachtman W, Pritchett E. *Manual for the Key Math Diagnostic Arithmetic Test*. Circle Pines, Minn: American Guidance Service; 1971.

16. Woodcock R. *Woodcock-Johnson Psycho-Educational Battery*. Boston, Mass: Teaching Resources; 1978.

17. Hessler GL. *Use and Interpretation of the Woodcock-Johnson PsychoEducational Battery*. Hingham, Mass: Teaching Resources Corp; 1982.

18. Slosson RL. *Slosson Intelligence Test (SIT) for Children and Adults*. East Aurora, NY: Slosson Educational Publications; 1963.

19. Achenbach TM, Edelbrock C. *A Manual for the Child Behavior Checklist and Revised Child Behavior Profile*. Queen City Printers; 1983.

20. Hollingshead AB. *Four Factor Index of Social Status*. New Haven, Conn: Yale University; June 1985. Working Paper.

21. SAS Institute Inc. *SAS User's Guide: Statistics; SAS User's Guide: Basics*. Cary, NC: SAS Institute Inc; 1982.

22. Hinckley RH. *Overview of Report #3: Student Economic and Educational Status and Receipt of Educational Services*. Washington, DC: Office of Education (Office of Planning, Budgeting, and Evaluation); 1979.

23. Bender BG, Belleau L, Fukahara JT, Mrazek DA, Strunk RC. Psychomotor adaptation in children with severe chronic asthma. *Pediatrics*. 1987;79:723-727.

24. Strunk RC, Mrazek DA, Fukuhara JT, Masterson J, Ludwick SK, La Brecque JF. Cardiovascular fitness in children with asthma correlates with psychological functioning of the child. *Pediatrics*. In press.

25. Stump N. Effects of steroid medication on school performance in asthmatic children. Presented at the Rocky Mountain Psychological Association Meeting; April 24, 1986; Denver, Colo.

26. Suess WM, Stump N, Chai H, Kalisker A. Mnemonic effects of asthma medication in children. *J Asthma*. 1986;23:291-296.

In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

Fenfluramine and Dextroamphetamine Treatment of Childhood Hyperactivity

Maureen Donnelly, MD; Judith L. Rapoport, MD; William Z. Potter, MD, PhD; Jerry Oliver; Cynthia S. Keysor; Dennis L. Murphy, MD (*Arch Gen Psychiatry*. 1989;46:205-212)

ARCHIVES OF INTERNAL MEDICINE

The Drug Approval Process at the Food and Drug Administration

Henry I. Miller, MD, Frank E. Young, MD, PhD (*Arch Intern Med*. 1989;149:655-657)

Cardiorespiratory Patterns During Alarms in Infants Using Apnea/Bradycardia Monitors

Ian Nathanson, MD; Jane O'Donnell, MSN; Mary F. Commins, BSN

• Evaluating the significance of alarms at home in infants monitored for apnea/bradycardia depends on subjective parental observations. Retrospective analysis of 165 event recordings made during alarms in 90 monitored infants indicated that alarms were due to prolonged (>15 s) apnea (6%), bradycardia (14%), shallow breathing (19%), mechanical malfunction (55%), or other causes (6%). Also, 68 infants had pneumograms. Of the 37 infants with an abnormal pneumogram, 14% had an abnormal event recording. Of the 31 infants with a normal pneumogram, 16% had an abnormal event recording. All monitors were discontinued without complication after a negative event recording. It may be concluded that (1) event recordings can document cardiorespiratory patterns during alarms, (2) the majority of alarms occurring at home are not significant, and (3) pneumograms do not appear to indicate which infants are at risk for a future significant alarm.

(*AJDC.* 1989;143:476-480)

Evaluating the effectiveness of home monitoring of apnea and/or bradycardia in infants relies heavily on information provided by parents with regard to frequency and type of alarms that occur in the home setting.[1,2] When an alarm is not witnessed clearly, parents are often unable to determine accurately whether an alarm was the result of true apnea and/or bradycardia,[3] or whether the alarm was triggered by shallow breathing associated with respiration below the threshold of detection of a monitor. Impedance monitors may alarm for apnea if breathing is too shallow to cause an impedance change that exceeds the threshold of the monitor. On the other hand, monitors may not detect true apnea if chest leads are placed near the cardiac impulse causing enough movement of the leads to result in an impedance change that exceeds the monitor's threshold.[4] Also, loose leads or other mechanical malfunction cause alarms.

Unless an infant requires vigorous stimulation or resuscitation, the inability of parents to report which alarms may be significant creates uncertainty about the appropriateness of further monitoring. This makes the decision to discontinue a monitor difficult if clinicians follow suggested guidelines that call for no alarms for 2 months.[5,6] There are no specific laboratory tests to aid in this decision, and pneumograms (PNGs) do not appear to predict which infants will be at risk for further apnea/bradycardia.[7,8]

We found it difficult to determine which alarms were truly significant and used event recorders in the home to aid us in this determination. To estimate the true frequency and types of alarms that occur in the home, we analyzed the cardiorespiratory patterns of alarms that were detected by event recorders in a series of infants who had been prescribed home monitors for a variety of indications.

SUBJECTS AND METHODS

Infants (N = 90) who were placed on monitors and referred to us for consultation for the diagnoses of persistent apnea of prematurity, apparent life-threatening event, being siblings of sudden infant death syndrome (SIDS) victims, having gastroesophageal reflux, episodes of cyanosis, or bradycardia were included in this study. These infants had event recordings done if the parents reported a history of multiple (more than three) apnea or bradycardia alarms during a routine follow-up visit.

The event recorder (Aequitron model 8293, Aequitron Medical Inc, Minneapolis, Minn) was placed in series with the apnea/bradycardia monitor (Aequitron model 8200) and recorded the date and time of the alarm as well as the respiratory and electrocardiographic (ECG) wave forms onto standard magnetic cassette tapes. The event recorder constantly stored data in its random access memory and was capable of recording onto tape respiratory and ECG patterns occurring 35 s before and 35 s after an alarm. The tapes were then converted to hard copy by a strip chart recorder (Aequitron model 8285) for visual analysis and interpretation.

Event recording tapes were reviewed and each alarm was examined for evidence of apnea and/or bradycardia. Bradycardia alarms were initiated when the heart rate had three successive R-R intervals that fell below the limit set for bradycardia. This process was reset each time a single R-R interval exceeded the bradycardia limit. In addition, the electrocardiographic tracing of bradycardia alarms was reviewed for signs of arrhythmia. An event recording tape was analyzed immediately if a parent reported using vigorous stimulation to terminate an alarm. Otherwise, an attempt was made to accumulate a series of alarms provided that an infant was clinically well.

An event recording was considered positive when one or more episodes of the following were noted: prolonged apnea greater than 15 s; heart rate lower than the preset monitor limits for an individual infant; or evidence of junctional or ventricular rhythm. All infants had their apnea limit set at 15 s. In general, infants had their bradycardia limits set at 80 beats per minute at age 1 month, 70 beats per minute at 2 months, and 60 beats per minute at 3 or more months. An event recording was considered negative when no alarms were noted for at least 4 weeks or when no evidence of prolonged apnea or bradycardia was seen or when there appeared to be a mechanical malfunction due to a loose lead that caused the monitor to alarm. Some families used electrode belts, while others

Accepted for publication December 20, 1988.

From the Department of Pediatrics, Division of Pediatric Pulmonology, State University of New York at Buffalo School of Medicine, and Children's Hospital of Buffalo.

Reprint requests to Nemours Children's Clinic, PO Box 5720, Jacksonville, FL 32247 (Dr Nathanson).

preferred stick-on electrodes placed inferior and lateral to the nipples. Shallow breathing was also considered to be insignificant and was defined as alarms associated with low amplitude signals that had a distinct respiratory pattern.

A total of 102 PNGs were also done in 68 of these infants. Many of these infants had at least one PNG ordered by the referring physician before we had seen the infants. The PNG recorded 12 hours of heart rate and respiration onto a magnetic cassette tape that was converted to hard copy by a PMD-12 (Oxford Medical Inc, Clearwater, Fla) and reviewed visually for central apnea, bradycardia, and percentage of periodic breathing. A PNG was considered abnormal if apnea (>15 s), bradycardia (<80 beats per minute), or excessive periodic breathing (>3%) was noted.

All parents had been instructed in appropriate use of monitors, including lead placement and alarm response by experienced nurse clinicians and vendors. Data are presented as mean ± SEM.

RESULTS

A total of 165 event recordings were made in 90 (52 male, 38 female) infants. Five other infants are not included in these data because their families were unable to understand how to use the equipment needed to make an event recording. The mean gestational age of the study population was 36.5 ± 0.4 weeks (range, 27.0 to 46.0 weeks), and the mean birth weight was 2660 ± 89 g (range, 967 to 4095 g). Monitors were prescribed for these infants for the following indications: persistent apnea of prematurity (37 of 90); sibling of a SIDS victim (15 of 90); apparent life-threatening event (16 of 90); apnea in a full-term

Table 1.—Monitor and Event Recording Data in 90 Infants

	Mean ± SEM
Monitor	
Age monitoring begun, wk (range)	6.3 ± 0.8 (0-41)
Duration of monitoring, wk (range)	19.0 ± 1.0 (5-50)
Event recorder	
Duration of event recording, (d)	19.7 ± 1.1
Alarms per recording*	
Total	19.7 ± 1.2 [100]
Apnea	1.1 ± 0.2 [6]
Bradycardia	2.8 ± 0.6 [14]
Shallow breathing	3.8 ± 0.4 [19]
Mechanical malfunction	11.1 ± 0.9 [55]
Other	. . . [6]

*Bracketed values are percents.

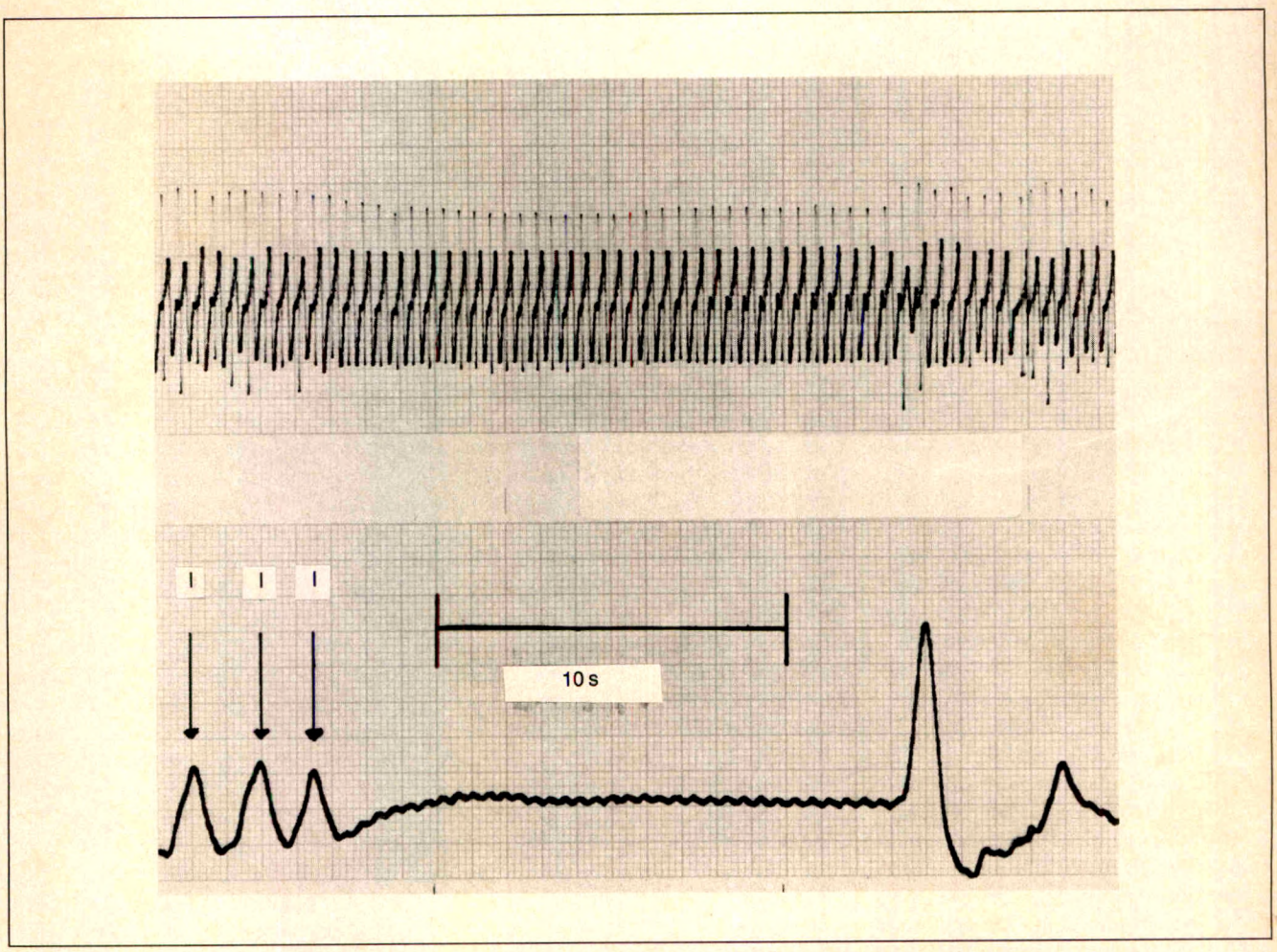


Fig 1.—Normal respiration followed by 16-s apnea without significant heart rate change. A deep inspiration terminates apnea. Upper tracing is electrocardiogram; lower tracing is respiration. I indicates inspiration.

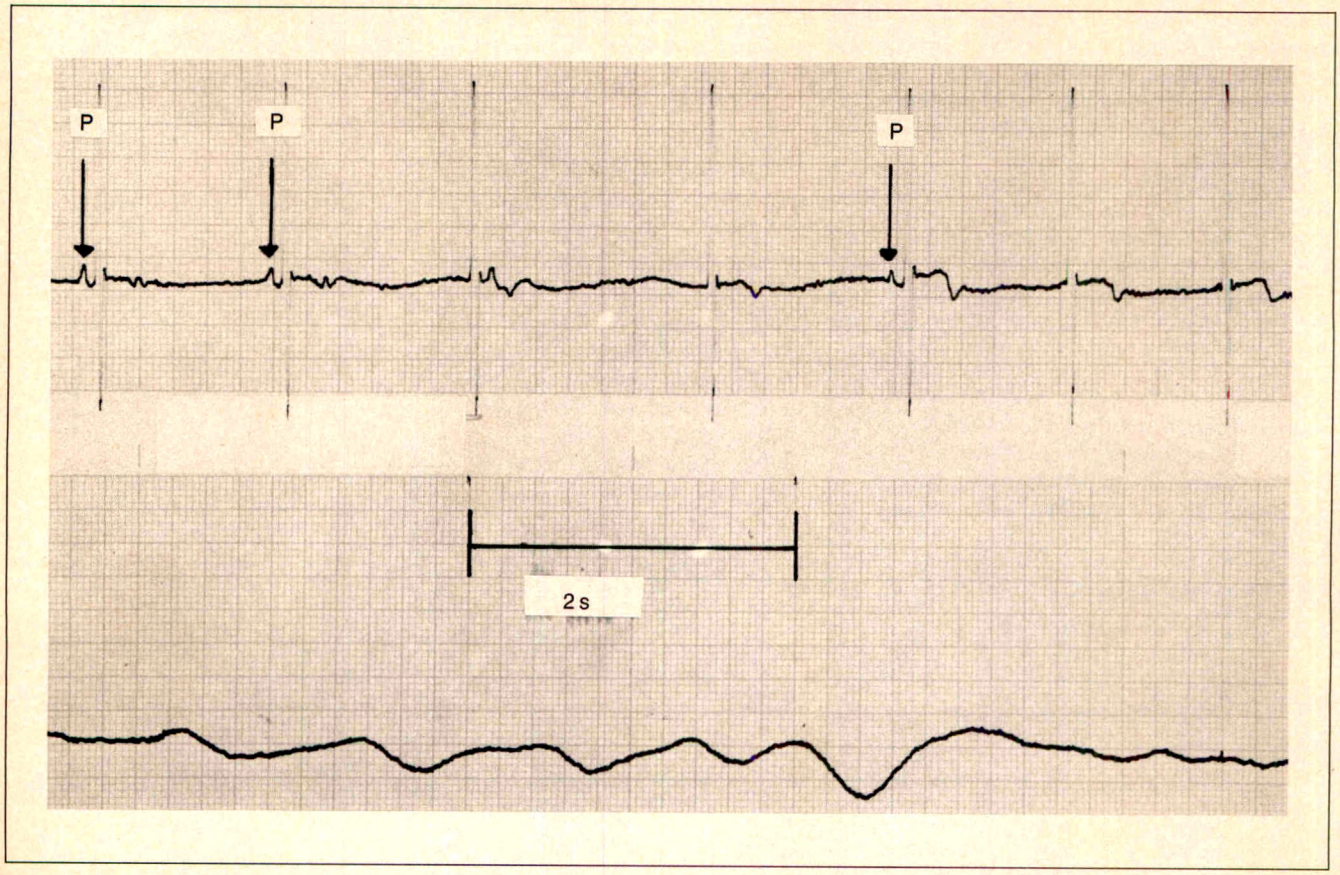


Fig 2.—Electrocardiogram tracing showing sinus and junctional rhythms characterized by presence and absence of P wave, respectively. Upper tracing is electrocardiogram; lower tracing is respiration.

infant (12 of 90); episode of unexplained cyanosis (3 of 90); recurrent bradycardia in nursery (2 of 90); pneumothorax in nursery (2 of 90); gastroesophageal reflux (2 of 90); or maternal drug addiction (1 of 90).

Home monitoring was initiated in these infants at a mean age of 6.3 ± 0.8 weeks (range, 0 to 41 weeks) and discontinued after 19.0 ± 1.0 weeks (range, 5 to 50 weeks) of monitoring. An average of 19.7 ± 1.2 alarms were detected during the 19.7 ± 1.1 days that the event recorders were used.

Of the 165 event recordings, 144 (87%) were negative, and 21 event recordings (13%) done in 13 infants were positive. Analysis of all episodes ($N = 3130$) on all event recordings indicated that 55% of the alarms were due to mechanical malfunction, and 19% were due to shallow breathing. The amount of shallow breathing may be overestimated because it could not be easily distinguished if low amplitude signals were due to poor lead placement or to true hypopnea. Significant apnea accounted for 6% of the alarms. Bradycardia alarms constituted 14% of the alarms, but many of these alarms were one to two beat pulse decelerations below the preset limit for bradycardia. Six percent of alarms could not be clearly determined or were due to combinations of loose leads and insignificant (<15 s) respiratory pauses. These data are summarized in Table 1.

Parents did not report abnormalities in their infants during alarms due to short pulse decelerations. Parents were instructed to stimulate infants if an alarm was audible for more than 10 s although they were often uncertain if cyanosis or pallor accompanied longer pulse decelerations or prolonged apnea. Parents of 47 of 90 infants kept log sheets describing the infant's condition and what intervention, if any, was taken during an alarm. Parents intervened in six cases where event recordings were positive and 15 cases where event recordings were negative. Parents did not intervene in four cases of positive event recordings and 25 cases of negative event recordings. One infant required resuscitation by the parents following an apnea of over 20 s. Examples of positive event recordings are shown in Figs 1 through 3 and demonstrate patterns of respiration and ECG that can be seen during real alarms.

A total of 102 PNGs were obtained in 68 of 90 infants. There were 49 abnormal PNGs noted in 37 infants, and 20 of 49 abnormal PNGs were due to excessive periodic breathing (range, 6% to 25%). In 5 (14%) of 37 infants there was an abnormal PNG and one or more positive event recordings. As shown in Table 2, 2 infants had junctional rhythm on their event recordings and bradycardia 50 to 53 beats per minute on PNG; 1 infant had junctional rhythm on event recording and 15% periodic breathing on PNG; 1 infant had prolonged apnea on event

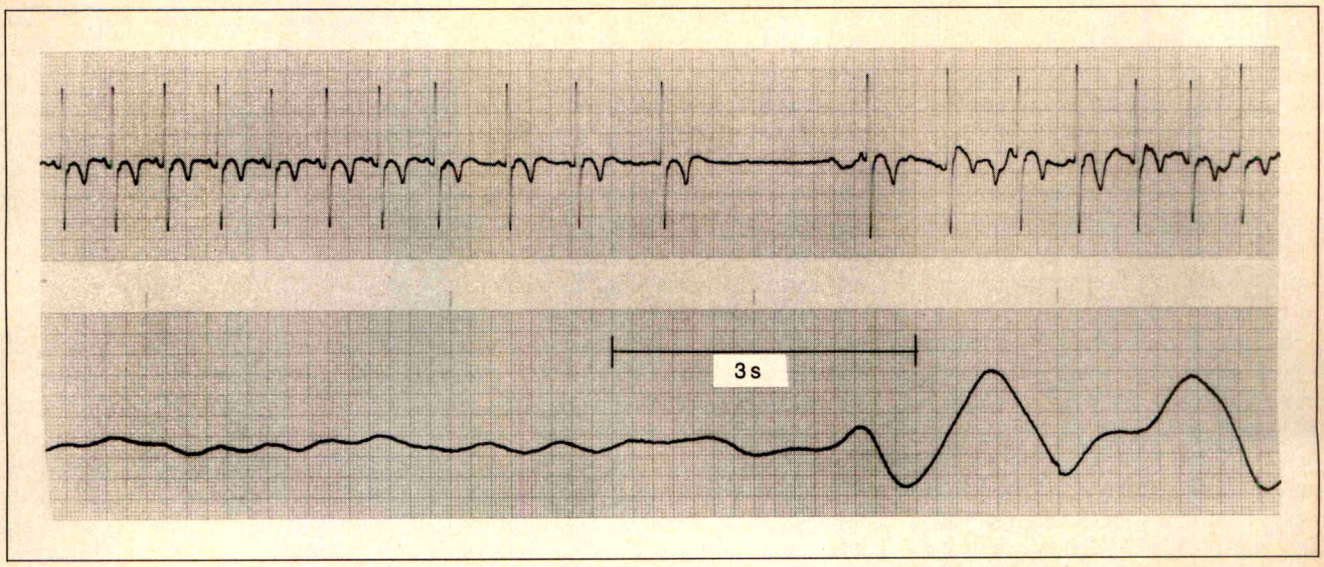


Fig 3.—Apnea associated with slowing heart rate and junctional rhythm. Following more than 2 s of asystole, sinus rhythm restarts. Upper tracing is electrocardiogram; lower tracing is respiration.

recording and 7% periodic breathing on PNG; 1 infant had three positive event recordings due to multiple episodes of prolonged apnea and three abnormal PNGs, which showed up to 23% periodic breathing and pulse decelerations to 58 beats per minute. All five of these infants had clinically significant gastroesophageal reflux although this was not the original indication for monitoring in any of these cases. Abnormal PNGs and only negative event recordings were seen in 32 (86%) of 37 infants.

There were 53 normal PNGs noted in 31 infants. In 5 (16%) of 31 infants there was a normal PNG and one or more positive event recordings, whereas 26 (84%) of 31 had normal PNGs and negative event recordings. Of the 22 infants who did not have a PNG, 2 (9%) of 22 had a positive event recording. These results are summarized in Table 3.

Table 2.—Summary of Results in Infants Who Had Positive Event Recordings and Abnormal Pneumograms

Case	Event Recording	Pneumogram
1	Prolonged apnea	Periodic breathing (7%)
2	Junctional rhythm	Periodic breathing (15%)
3	Junctional rhythm	Bradycardia
4	Prolonged apnea	Periodic breathing (23%) Bradycardia
5	Junctional rhythm	Bradycardia

Table 3.—Results of Event Recordings and Pneumograms (PNGs)

	No. of Infants	Positive Event Recording	Negative Event Recording
Abnormal PNG	37*	5	32
Normal PNG	31†	5	26
No PNG	22	2	20

*There were 49 abnormal PNGs in 37 infants.
†There were 53 normal PNGs in 31 infants.

COMMENT

This study indicates that event recordings provide objective information about frequency and types of alarms that infants have while using apnea/bradycardia monitors. Only 14% of infants in this study had positive event recordings, and several of these infants had multiple positive event recordings, suggesting that a small group of infants do have repeated episodes of apnea and/or bradycardia. The vast majority of alarms appeared to result from either shallow breathing or mechanical malfunction despite reinforcement of proper use of equipment. Previous reports estimated that over 80% of alarms were noted while a child appeared to be breathing normally,[9,10] and it was assumed that these alarms were false alarms. Our data support this assumption.

Although one infant required resuscitation, two other infants had prolonged apnea and one had marked bradycardia without exhibiting physical signs (eg, cyanosis) that usually prompt parents to stimulate the infant. The reliability of parental observations in monitored infants is unclear. Our results indicated that 52% of parents kept log sheets. In this group, 32% reported intervening during alarms that were demonstrated

not to be significant, and 9% did not intervene during an alarm that was significant on event recording. This finding suggests that parents may be unwilling to restrain from intervening during an alarm and/or are not able to judge whether an alarm is significant. Although this approach is understandable from a parent's viewpoint, it complicates physician interpretation of information presented by the parents.

In four of five infants with abnormal PNGs and subsequent positive event recordings, the abnormality noted on PNG was similar to the abnormality noted on event recording. However, the percentage of infants with both positive event recordings and abnormal PNGs was similar to that for infants with positive event recordings and negative PNGs. Thus, PNGs did not appear to predict which infants would have a positive event recording. Whether event recordings predict future alarms is not clear although several infants had more than one positive recording. Event recordings do not supply data about periodic breathing or respiratory/ECG trends over prolonged intervals and would not be appropriate to test for these patterns.

There were no complications from discontinuing a monitor if an event recording was negative, and no infant had an acute life-threatening event, had clinical apnea or bradycardia, or died for at least 12 months after the monitor was discontinued. The results of PNGs did not influence our decision to continue or to stop monitoring in contrast to recommendations made by others.[11]

It is not clear whether event recordings can reduce duration of monitoring. Also, it is not known if asymptomatic episodes of prolonged apnea or short, self-resolved pulse decelerations that fall below the arbitrary bradycardia limit indicate alarms that have clinical significance. Similarly, it is also unclear what level of bradycardia is acceptable. Asymptomatic bradycardia to less than 50 beats per minute with junctional rhythm was detected in a sleeping infant in whom no intervention was used. Similar findings have been reported in adults.[12] The length of monitoring of infants in this study was similar to other centers that reported monitoring infants for 4 to 9 months[13,14] and our siblings of SIDS victims were monitored routinely until 6 months of age.

Event recordings appear to provide useful information to clinicians for assessment of infants whose monitors alarm frequently. In view of the increased parental anxiety of monitored infants[10,15] and debate about the cost-effectiveness and efficacy of monitoring,[16] documentation of alarms that are not significant may lead to earlier cessation of monitoring and substantial savings of health care dollars.

The authors acknowledge the technical help of Molly Fox and manuscript preparation by Roseann McAnulty.

References

1. Brooks JG. Apnea of infancy and sudden infant death syndrome. *AJDC*. 1982;136:1012-1023.
2. Duffty P, Bryan MH. Home monitoring in near-miss sudden infant death syndrome (SIDS) and in siblings of SIDS victims. *Pediatrics*. 1982;70:69-74.
3. Krongrad E, O'Neill L. Near-miss sudden infant death syndrome episodes? A clinical and electrocardiographic correlation. *Pediatrics*. 1986; 77:811-815.
4. Southall DP, Richards JM, Lau KC, Shinebourne EA. An explanation for failure of impedance apnea alarm systems. *Arch Dis Child*. 1980; 55:63-65.
5. Brown LW. Home monitoring of the high risk infant. *Clin Perinatal*. 1984;11: 85-100.
6. Spitzer AR, Fox WW. Infant apnea: an approach to management. *Clin Pediatr*. 1984;34:374-380.
7. Southall DP, Richards JM, de Swiet M, et al. Identification of infants destined to die unexpectedly during infancy: evaluation of predictive importance of prolonged apnea and disorders of cardiac rhythm or conduction. *Br Med J*. 1983;286:1092-1096.
8. Davidson Ward SL, Keens TG, Chan LS, et al. Sudden infant death syndrome in infants evaluated by apnea programs in California. *Pediatrics*. 1986;77:451-458.
9. Kahn A, Blum D. Home monitoring of infants considered at risk for the sudden infant death syndrome. *Eur J Pediatr*. 1982;139:94-100.
10. Emery JL, Waite AJ, Carpenter RG, Limerick SR, Blake D. Apnea monitors compared with weighing scales for siblings after cot death. *Arch Dis Child*. 1985;60:1055-1060.
11. Oren J, Kelly D, Shannon DC. Identification of a high risk group for sudden infant death syndrome among infants who were resuscitated for sleep apnea. *Pediatrics*. 1986;77:495-499.
12. Guilleminault C, Pool P, Motta J, Gillis AM. Sinus arrest during REM sleep in young adults. *N Engl J Med*. 1984;311:1006-1010.
13. Ariagno RL, Guilleminault C, Korobkin R, Owen-Boeddiker M, Baldwin R. Near-miss for sudden infant death syndrome infants: a clinical problem. *Pediatrics*. 1983;71:726-730.
14. Mackay M, Abreu FA, Silva E, MacFadyen UM, Williams A, Simpson H. Home monitoring for central apnea. *Arch Dis Child*. 1984;59:136-142.
15. Cain LP, Kelly DH, Shannon DC. Parents' perceptions of the psychological and social impact of home monitoring. *Pediatrics*. 1980;66:37-41.
16. American Academy of Pediatrics. Task force on prolonged infantile apnea: prolonged infantile apnea, 1985. *Pediatrics*. 1985:76:129-131.

In Other AMA Journals

ARCHIVES OF DERMATOLOGY

Granulomatous Perioral Dermatitis in Children

Ilona J. Frieden, MS; Neil S. Prose, MD; Van Fletcher, MD; Maria L. Turner, MD (*Arch Dermatol*. 1989;125:369-373)

Kaposi's Sarcoma in a 6-Day-Old Infant With Human Immunodeficiency Virus

Patricia Gutierrez-Ortega, MD; Sagrario Hierro-Orozco, MD; Rodolpho Sanchez-Cisneros, MD; Felix Cuevas; Luis F. Montano, MD (*Arch Dermatol*. 1989;125:432)

Use of Adrenergic Bronchodilators by Pediatric Allergists and Pulmonologists

Richard W. Newcomb, MD

• Twenty-one pediatricians specializing in allergy, pulmonology, or both were questioned about their use of adrenergic bronchodilators for treating children of different ages at home, in the emergency department, and in the hospital. Most would use inhaled medications in all settings and for all ages. Few expressed strong preference for one drug over another, but only 2 would regularly use nebulized isoproterenol hydrochloride or isoetharine hydrochloride. Dosing frequency of inhaled medication at home was usually limited to every 4 hours, but in the emergency department or hospital, intervals between doses of 20 minutes or less were common. If this treatment failed, 9 physicians would use intravenous isoproterenol, but 4 strongly opposed its use. These results indicate that substantial variation exists in current expert practice, but that inhaled albuterol, metaproterenol, or terbutaline sulfate are most often preferred for treating asthma, bronchopulmonary dysplasia, and bronchiolitis in children of all ages, and that doses and dosing intervals are frequently altered to meet patient needs.

(*AJDC.* 1989;143:481-485)

Most current textbook recommendations for the use of adrenergic bronchodilators in children[1-6] appear to be unsatisfactory, chiefly because most fail to convey how usage may vary in different settings. By concentrating on use at home, most recommendations seem timid in comparison with what personal experience and published works[7-10] indicate to be common practice in treating hospitalized patients. However, practices not supported by textbook or manufacturers' recommendations tend to encounter resistance. The matter is complicated because the pharmaceutical companies that supply albuterol sulfate, metaproterenol sulfate, isoetharine hydrochloride, and terbutaline sulfate have not obtained federal Food and Drug Administration approval to market them for inhalation by patients less than 12 years of age.

Therefore, to document current usage by those practitioners with the widest experience and expertise and to find areas of agreement and controversy, 21 American academic pediatricians were surveyed who specialize in allergy and/or pulmonology. The results indicate substantial variation in practice, but also agreement on a few important issues.

SUBJECTS AND QUESTIONNAIRE

Subjects

In the first half of 1987, I personally contacted pediatric allergist-immunologists and pulmonologists from medical school faculties in 17 states. Most were directors of training programs in allergy-immunology or pulmonology or were otherwise academically prominent. Ten allergists were contacted and 8 agreed to the 30- to 45-minute telephone interview, while 2 deferred to members of their faculties who they thought would be more suitable. Eleven pulmonologists were contacted. Seven agreed to be interviewed, 1 deferred to a colleague, and 3 who did not agree were replaced. The final group of 21 included 10 pediatric allergist-immunologists (1 primarily a pharmacologist and 1 a clinical immunologist), 9 pulmonologists, and 2 pediatricians who were board-certified in both allergy-immunology and pediatric pulmonology.

All subjects were members of medical school faculties, 17 full-time and four part-time. Eighteen devoted at least 20 hours a week to patient care, and at least 80% of the patients of 16 physicians were children who received bronchodilators. Anonymity was offered to all respondents, but few requested it.

Questionnaire

Devised with the help of an experienced health surveyor, the questionnaire was revised after trial use with two physicians not in the series. Further slight revisions were made for clarity and speed after the first five interviews. Copies of the final instrument are available on request.

Questions were directed at learning the interviewees' usual practices in using adrenergic bronchodilators for treating asthma in the patient's home, the emergency department, and the hospital, both for acute, severe asthma ("status asthmaticus") and for early respiratory failure. The example used for respiratory failure was of a child admitted with signs of severe obstruction from asthma not responding well to standard therapy. The hypothetical child was still alert and strong, and had arterial blood pH of 7.30, P_{CO_2} of 50 mm Hg and P_{O_2} of 45 mm Hg while breathing room air. Questions were stratified as to age groups: 13-year-old patients, 7-year-old patients, 18-month-old patients, and 5-month-old patients.

Further responses were specifically sought about management of rapid sinus tachycardia during treatment with adrenergics, and about the use of these drugs for children with bronchopulmonary dysplasia and bronchiolitis. At the end of each segment of structured questions, I asked open-ended questions about problems encountered in using bronchodilators as described, and about exceptions to the usual practice. A final invitation was given to offer free-form comments on the subjects covered.

Statistical Methods

Group differences were compared using uncorrected χ^2 analysis. For group comparisons, the two pediatricians board-certified in both subspecialties were grouped with pulmonologists. Significance was accepted at $P<.05$.

RESULTS

Doses in All Settings

When using metered-dose inhalers (MDIs), two or three puffs (actuations) were prescribed per dose. The subcutaneous dose of epinephrine hydrochloride or terbutaline sulfate was always 0.01 mg/kg, with a maximum dose of 0.3 to 0.4 mg.

The amount of bronchodilator added

Accepted for publication December 27, 1988.

From the Pediatric Allergy and Pulmonology Service, Merrillville, Ind.

Reprint requests to the Pediatric Allergy and Pulmonology Service, 8683 Connecticut St, Merrillville, IN 46410 (Dr Newcomb).

to nebulizers varied widely, depending on the drug, patient age, and, to a much lesser extent, on the setting. Doses usually used are presented in Table 1, which combines recommendations for patients in all settings. (Numerals represent the number of times the indicated dose was recommended). When doses were specified without reference to body weight, they were only loosely related to patient age. When expressed as milligram per kilogram of body weight, maximum milligram doses were sometimes specified, but for patients in respiratory failure some physicians would titrate the dose according to the patients' response rather than set arbitrary milligram limits.

Table 1.—Dose Choices for Nebulized Bronchodilators

Bronchodilator*	No. of Times Indicated Dose Was Recommended by Patient Age			
	13 y	7 y	18 mo	5 mo
Albuterol sulfate				
0.5-0.75 mg	0	0	1	1
1.25-2.5 mg	5	5	5	4
0.1 mg/kg	6	6	7	6
0.15 mg/kg	5	5	7	8
Metaproterenol sulfate				
5 mg	0	1	4	4
10 mg	3	4	4	5
15 mg	3	1	2	2
50 mg†	3	3	3	3
0.5 mg/kg	9	11	11	13
Terbutaline sulfate				
1 mg	3	3	3	5
2 mg	3	4	6	4
3 mg	2	2	1	0
5 mg	2	5	0	0
0.1-0.2 mg/kg	0	0	0	4
Maximum doses				
Metaproterenol		**Albuterol**		**Terbutaline**
15 mg 26		2.5 mg 15		5.0 mg 1
25 mg 4		5.0 mg 30		No milligram limit‡ 14
50 mg† 12		No milligram limit‡ 4		

*See "Results" section for explanation of doses.
†Hospital use only.
‡Respiratory failure only.

Use at Home

Route of Administration.—For the normal 13-year-old patient, all respondents would prescribe MDIs to deliver bronchodilators, and all but one would also use them for 7-year-old patients (Table 2). One pulmonologist preferred nebulizers for treating most 7-year-old patients, and another did so for children of any age with a history of repeated emergency department visits or hospital admissions. For 18-month-old and 5-month-old patients, nebulized medications were used by all but four allergists and one pulmonologist, who would use oral bronchodilators. Subcutaneous epinephrine or terbutaline were mentioned by only two respondents for home use during emergencies in remote settings, using "conservative" guidelines.

Spacers or holding chambers were used by only 3 respondents for most of their 13-year-old patients, but by 12 for most 7-year-old patients. Eleven physicians would use them for most children younger than age 7 years using MDIs.

Drugs for Home Use.—Albuterol via MDI for 13-year-old and 7-year-old patients and metaproterenol by nebulizer for younger patients were the usual choices (Table 2). Strong preference for any drug was rare, and one physician usually chose whatever samples were available.

Frequency of Dosing.—Adrenergics as maintenance drugs (Table 2) were used only in conjunction with theophylline, cromolyn sodium, or corticosteroids. For home treatment of symptoms, 7 physicians generally limited use to two to four doses a day, whereas 12 advised 4-hour intervals between doses. Four physicians usually allowed home treatments every 1 to 3 hours, but if the parents were "well-trained," or were kept in "close telephone contact," 6 more would increase the frequency to every 1 to 2 hours.

Problems With Home Use.–Six physicians reported "none or few" problems with their use of adrenergics at home. Seven mentioned tremor, palpitations, or "hyper" behavior, and two listed minor tachycardia. Abuse, or over-dependence on inhaled adrenergics, to the exclusion of other measures or leading to delays in seeking medical care, were mentioned by eight physicians. Two physicians volunteered that nebulizers caused difficulties for some parents, and two others noted that parents of younger children sometimes overextended and exhausted themselves using nebulized bronchodilators at home.

Two allergists felt that oral agents afforded poor relief of symptoms and that oral dosage guidelines were unsatisfactory. However, the longer duration of action made oral adrenergics preferable to inhaled drugs for use at bedtime in the view of another allergist.

Emergency Department Use

Drug and Route.—For the average child with asthma in the emergency department, nebulized drugs (albuteral, metaproterenol, or terbutaline) were the first choice of five allergists and nine pulmonologists (Table 3). Subcutaneous epinephrine or terbutaline would be used by six or seven allergists for patients of different ages, compared with one or two of the pulmonologists. This difference between allergists and pulmonologists was significant ($P<.025$) in the case of 5- and 18-month-old infants. Three physicians who often initiated treatment with subcutaneous injections would, however, switch to the nebulized route for subsequent doses. Epinephrine (Sus-Phrine), given only after initial relief of obstruction, was mentioned three times.

Many physicians expressed a willingness to change the initial drug or its route of administration in response to preferences of colleagues or parents, but more often in response to the failure

to obtain relief of airway obstruction. In the latter case, five would switch to nebulized terbutaline, three to subcutaneous epipinephrine or terbutaline, and four would add atropine sulfate to a subsequent dose of the nebulized adrenergic agent.

Dosing Frequency.—Fourteen respondents (six allergists and eight pulmonologists) would allow no more than 20 minutes to elapse between doses, and six specified 30- to 60-minute intervals, irrespective of the medication, route, dose, or patient age (Table 3). Two allergists, however, chose dosing intervals of 4 hours, one for all ages, and the other for 5-month-old infants only.

Problems.—A frequent complaint was the physicians' frustration in trying to influence the management of childhood asthma in their own institutions. Only twice was disagreement with emergency department physicians held responsible, while 10 times it was the unavailability or unwillingness of respiratory therapists to spend time with children receiving nebulized medications.

Other problems included tremor, tachycardia, emesis, and "hysterical reactions" to the injection of epinephrine. The tachycardia was often dismissed as trivial, and one respondent noted that heart rate usually decreased with effective treatment. To minimize cardiac effects in his patients with known "cardiac problems," another physician would use nebulized terbutaline.

Use In Hospital

Acute, Compensated Asthma.—*Drug and Route.*—For treatment of status asthmaticus without respiratory failure, 20 of 21 respondents would use nebulized adrenergic bronchodilators, most often metaproterenol, for all age groups (Table 4). One clinical immunologist would use nebulized adrenergic agents only for children unresponsive to aminophylline.

If response to the first-chosen bronchodilator was unsatisfactory, 18 physicians sometimes or often switched drugs, usually to nebulized albuterol or terbutaline, but in two cases the switch was to subcutaneous epinephrine or terbutaline. Two physicians often added nebulized atropine sulfate to the adrenergic agent.

Table 2.—Home Use of Bronchodilators

Use of Bronchodilator	Patient Age 13 y	7 y	18 mo	5 mo
Route				
Inhaled				
Metered-dose inhaler	21	20	0	0
With Inspirease	3	10	0	0
With Aerochamber	0	2	0	0
Nebulizer	0	1	16	15
Oral	0	0	4	5
Did not know	0	0	1	1
Drug				
Albuterol sulfate	16	15	8	8
Metaproterenol sulfate	4	5	12	10
Terbutaline sulfate	1	1	0	2
Isoetharine hydrochloride	0	0	0	1
Did not know	0	0	1	1
Frequency				
Maintenance				
4 times/d	4	4	5	5
3 times/d	3	3	3	3
2 times/d	1	1	2	2
Home treatment of symptoms				
1 h	0	0	1	1
2-3 h	2	2	3	3
4 h	12	12	6	5
4 times/d	5	4	4	6
3 times/d	1	1	4	3
2 times/d	1	1	2	2

Table 3.—Emergency Department Use of Bronchodilators

Use of Bronchodilator	Patient Age 13 y	7 y	18 mo	5 mo
Drug and route				
Nebulized				
Albuterol sulfate	6	6	6	6
Metaproterenol sulfate	6	5	5	7
Terbutaline sulfate	2	2	1	1
Subcutaneous				
Epinephrine hydrochloride	6	7	8	6
Terbutaline	1	1	1	1
Frequency				
≤20 min	14	15	16	16
30-45 min	4	4	3	2
60 min	2	1	1	1
4 h	1	1	1	2

Frequency.—Approximately equal numbers of physicians chose initial dosing frequencies of 20 minutes, 1 to 2 hours, and 3 to 4 hours (Table 4). In this respect, treatment did not differ with patient age or between allergists and pulmonologists.

Respiratory Failure.—*Drug, Route, and Frequency.*—Twenty respondents would treat early respiratory failure from asthma with nebulized adrenergic agents (Table 4). The drugs chosen usually were the same as used for compensated asthma, but seven would begin treatment using inhaled terbutaline, and one pulmonologist would use nebulized isoproterenol. One allergist would start the intravenous infusion of isoproterenol at once.

The most important accommodation

Table 4.—Use of Bronchodilators in the Hospital

	Patient Age			
	13 y	7 y	18 mo	5 mo
Severe asthma				
Drug and route				
Nebulized				
Albuterol sulfate	6	6	6	6
Metaproterenol sulfate	10	10	10	9
Terbutaline sulfate	4	4	4	4
Isoetharine hydrochloride	0	0	0	1
None	1	1	1	1
Frequency				
≤20 min	5	5	5	5
1-2 h	6	6	6	6
3-4 h	7	7	7	6
4-6 h	2	2	2	3
Respiratory failure				
Drug and route				
Nebulized				
Albuterol	5	5	5	4
Metaproterenol	7	7	7	6
Terbutaline	7	7	7	7
Isoproterenol hydrochloride	1	1	1	1
Intravenous isoproterenol	1	1	1	1
Frequency (nebulized doses)				
≤20 min	14	14	13	13
30 min	3	3	4	4
4 h	3	3	3	2

to the presence of respiratory failure was a substantial increase in the frequency of nebulized treatments (Table 4). Intervals of 30 minutes or less would be used by 17, 14 of whom specified use either "continuously" or every 10 to 20 minutes (10 pulmonologists and 4 allergists, $P<.05$). Three allergists would use a 4-hour dosing schedule.

If patients with respiratory failure should not improve or should become worse despite treatment, 15 respondents reported changing the drug or route of administration. Four would add atropine to the nebulized adrenergic agent. Seven would switch to a different nebulized adrenergic bronchodilator (3 to albuterol, 2 to terbutaline, and 1 each to metaproterenol or isoetharine). Nine respondents might add or substitute intravenous isoproterenol when nebulized bronchodilators failed, and 1 allergist initiated treatment with it. Citing complications of its use,[11] however (one characterized it as "the worst possible therapy"), 4 respondents would prefer to use mechanically assisted ventilation, and 3 others would use subcutaneous or intravenous terbutaline.[8,12]

Problems.—The use of inhaled adrenergics at very frequent intervals was associated with "no problems" in the experience of seven respondents. Ten thought that sinus tachycardia was sometimes a problem, but five of these volunteered that it was not serious ("more a problem for the parents than the child," said one), and two specified that "serious cardiac problems" had not been seen even with aggressive use of nebulized adrenergics. One allergist, however, recalled a case in which lidocaine hydrochloride had been given to treat frequent premature ventricular contractions in a child receiving nebulized metaproterenol. A pulmonologist had observed either paroxysmal atrial tachycardia or ventricular tachycardia in a patient with cystic fibrosis treated with an unspecified nebulized adrenergic agent.

To explore this issue further, a separate question was asked about a hypothetical 18-month-old child whose heart rate exceeded 190 beats per minute during treatment for a severe episode of asthma. Eleven (4 allergists and 7 pulmonologists) would continue their therapy without change, 1 asserting that tachycardia is more likely to result from under treatment of asthma than overtreatment. Nevertheless, 5 of these 11 volunteered that they would not increase the dose further if the heart rate exceeded 200 to 220 beats per minute, and 1 would be "more cautious" if the patient were 18 years old rather than 18 months old. Ten respondents would modify treatment: 5 would stop or temporarily interrupt delivery of adrenergics at a heart rate over 190, and another 5 would reduce its frequency or dose (at least, added 3, if they thought the drug responsible for the tachycardia). Close monitoring of patients was commonly emphasized ". . . and not just using a machine," added 1 allergist).

Aggravation of hypoxemia by adrenergics was listed as a problem by only three respondents, perhaps because most had either implied or specified the use of supplemental oxygen. Two respondents had observed worsening of bronchoconstriction that was apparently induced by nebulized agents. Other problems mentioned were tremor, agitation, anxiety, and intolerance of the nebulizer face mask. Interdepartmental problems with respiratory therapy or pharmacy were mentioned twice.

Bronchopulmonary Dysplasia and Bronchiolitis.—Infants with bronchoconstriction caused by bronchopulmonary dysplasia would receive adrenergic bronchodilators as for asthma from 17 of the physicians. Eighteen would also use the drugs to treat bronchiolitis, but 5 of these would require some indication that the obstruction was improved after a trial treatment period of up to 24 hours. Three would be less aggressive in treating bronchiolitis than asthma, 1 substituting inhaled atropine for some doses of adrenergics.

COMMENT

Data presented here illustrate that there is no universally accepted practice in the use of adrenergic bronchodilators in childhood asthma. Nevertheless, broad agreement did emerge in favor of using inhaled agents and, with appropriate monitoring, varying the dosage according to patient needs. Most of the physicians surveyed would accept a certain level of tremor and sinus tachycardia, and none would hesitate to use available medications for treating children under 12 years old. With some

qualifications, most would also treat bronchiolitis and bronchopulmonary dysplasia with the same bronchodilators.

Of the observed diversity of practice, only a fraction could be attributed to differences between these allergists and pulmonologists. The allergists were slightly more likely than the pulmonologists to prescribe oral than nebulized bronchodilators for home treatment of infants, and were significantly more likely to use subcutaneous bronchodilators in the emergency department. In treating early respiratory failure from asthma, pulmonologists also used nebulized bronchodilators at significantly higher frequency than allergists, although experience published in the allergy literature[7-10] describes favorable experience with aggressive dosing.

Other practices, including the choice of adrenergic drug, were unrelated to subspecialty. In all settings, albuterol, metaproterenol, and terbutaline were most commonly used. There was a trend toward using metaproterenol for younger children and terbutaline for hospitalized patients, particularly those in respiratory failure and for whom other drugs had failed or presented problems. Albuterol was newly available in this country at the time of the survey, and an intention to use it was repeatedly expressed by those not yet doing so. Most respondents volunteered that they would switch drugs and/or add nebulized atropine if response to the first drug was unsatisfactory, but nebulized isoetharine and isoproterenol were preferred by only two respondents, and then for limited indications. Intravenous isoproterenol was reserved for treatment of respiratory failure, and then only after other measures failed. Sharp disagreement surfaced over its use, however, and several respondents would prefer to use subcutaneous or intravenous terbutaline[8,12] or mechanically assisted ventilation.

Questions about dosage of nebulized drugs were answered in terms of milliliters, milligrams, or milligrams per kilograms of body weight, either with or without explicit limits for heavier patients. Such inexact dosing is to be expected for a route of administration subject to as many variables as nebulization.[13] In this country, dosage guidelines for children under the age of 12 years are not available from the manufacturers of albuterol, metaproterenol, or terbutaline. Not one of the respondents, however, mentioned the absence of approval by federal agencies as a factor in their choice of drug or dosage.

The high doses and frequencies described with which nebulized adrenergics were used with relative impunity may come as a surprise to many pediatricians. Textbook recommendations and manufacturer guidelines are almost uniformly more restrained than most current expert use would appear to support. Even in the home setting, some physicians advised dosing frequencies exceeding the popular 4-hour limits. Close monitoring of patients seemed to be fundamental to the choice of dosage and frequencies, in whatever setting it was to occur.

The common use of adrenergic bronchodilators, albeit with some qualifications, in treating bronchopulmonary dysplasia and bronchiolitis may also be of interest to general pediatricians, considering the controversy whether infants can respond to bronchodilators.[14,15]

The wide variety of practices revealed here is matched by the wide differences of severity and responsiveness to treatment of childhood asthma. The tendency for the pulmonologists to use higher levels of treatment than the allergists may thus simply reflect their greater involvement with patients in intensive care. However, factors other than severity may also determine practice styles, and if reluctance to deviate from common practice or manufacturers' recommendations should cause any physician to withhold needed treatment, data presented here might allay such fears and also help convince ancillary personnel to modify any arbitrary restrictive practices.

Other physicians may chose to continue restricting their use of bronchodilators out of real concerns for the safety of using them as aggressively as many of our respondents described. This series was, admittedly, small and may have missed some significant adverse reactions. To respond to such concerns, future research could follow two lines: active surveillance to collect anecdotal reports of adverse reactions, and prospective studies of treatment outcomes by centers utilizing more aggressive treatment protocols, for comparison with those of centers utilizing more restrictive guidelines. If patient mix and nonadrenergic aspects of therapy could be controlled, the results of such comparative studies could provide convincing recommendations for treatment and monitoring appropriate to the widely differing levels of morbidity seen in childhood asthma.

This study was supported in part by a grant from CIBA-Geigy Corporation, Summit, NJ.

I thank the physicians who freely gave their time for this study.

References

1. Bierman CW, Pearlman DS. Asthma. In: Kendig EL Jr, Chernick V, eds. *Diseases of the Respiratory Tract in Children*. Philadelphia, Pa: WB Saunders Co; 1983:535.

2. Chantarojanasiri T, Nichol DG, Rogers MC. Lower airway disease: bronchiolitis and asthma. In: Rogers MC, ed. *Textbook of Pediatric Intensive Care*. Baltimore, Md: Williams & Wilkins; 1987:216.

3. Isles AF, Levison H. Pediatric asthma. In: Weiss EB, Segal MS, Stein M, eds. *Broncial Asthma: Mechanisms and Therapeutics*. Boston, Mass: Little Brown & Co Inc; 1988:857-871.

4. Fireman P. Status asthmaticus in children. In: Middleton E Jr, Reed CF, Ellis EF, eds. *Allergy: Principles and Practice*. St Louis, CV Mosby Co; 1983:997-1002.

5. Eggleston PA, Banks JR. Asthma in children. In: Lichtenstein LM, Fauci AS, eds. *Current Therapy in Allergy, Immunology and Rheumatology: 1985-1986*. St Louis, Mo: CV Mosby Co; 1985:23-27.

6. Ellis EF. Allergic disorders: asthma. In: Behrman RE, Vaughan VC III, eds. *Nelson Textbook of Pediatrics*. Philadelphia, Pa: WB Saunders Co; 1983:539-547.

7. Moller FW, Hurwitz ME, Custer JR. Improvement in clinical asthma score and PaCO2 in children with severe asthma treated with continuously nebulized terbutaline. *J Allergy Clin Immunol*. 1988;81:1101-1109.

8. Tipton WR, Nelson HS. Frequent parenteral terbutaline in the treatment of status asthmaticus in children. *Ann Allergy*. 1987;58:252-256.

9. Garra B, Shapiro GG, Dorsett CS, Simons FE, Pierson WE, Bierman CW. A double-blind evaluation of the use of nebulized metaproterenol and isoproterenol in hospitalized asthmatic children and adolescents. *J Allergy Clin Immunol*. 1977;60:63-68.

10. Lenny W: Nebulized salbutamol in the treatment of acute asthma in children. *Lancet*. 1978;1:440-441.

11. Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion of intravenous isoproterenol. *J Allergy Clin Immunol*. 1979;63:407.

12. Cheong B, Reynolds SR, Rajan G, Ward MJ. Intravenous β agonist in severe acute asthma. *Br Med J*. 1988;297:448-450.

13. Kelly HW. Pharmacotherapy of pediatric lung disease: differences between children and adults. *Clin Chest Med*. 1987;5:681-694.

14. Silverman M. Bronchodilators for wheezy infants? *Arch Dis Child*. 1984;59:84-87.

15. Mallol J, Barruento L, Giardi G, et al. Use of nebulized bronchodilators in infants under 1 year of age: analysis of four forms of therapy. *Pediatr Pulmonol*. 1987;3:298-303.

Sports Medicine

William B. Strong, MD, Augusta, Ga
Carl L. Stanitski, MD, Pittsburgh, Pa
Ronald E. Smith, PhD, Seattle, Wash
Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*The use of illicit drugs among athletes as well as nonathletes has received great notoriety following the 1988 Summer Olympics. The current study has documented the knowledge, attitudes, and behaviors of high school students in the Midwest. It is recognized that a significant portion of users received the drugs from health professionals. It is critical that the pediatric community voice its strong opposition to the use of anabolic steroids and other ergogenic agents. Youths must understand that there are no innocuous magic bullets. Improvement should be on the basis of physical training, proper nutrition, and mental preparedness.*—W.B.S.

High School Athletes and the Use of Ergogenic Aids

Daniel P. Krowchuk, MD; Trina M. Anglin, MD, PhD; Donald B. Goodfellow, MD; Terry Stancin, PhD; Paul Williams, MD; Gregory D. Zimet, PhD

• To determine high school athletes' attitudes toward and use of ergogenic aids, we surveyed 295 students presenting for preparticipation examinations. In general, young athletes believed that steroids and amphetamines were not efficacious in enhancing sports performance and that their use was potentially harmful. Subjects reported minimal use of steroids (1%) and amphetamines (2%), and only a minority would consider their use. As a group, however, male athletes were more likely to believe that steroids were effective (32% vs 13%) and to consider the future use of these agents (14% vs 0) compared with female athletes. The majority of high school athletes believed that supplemental protein or vitamins could improve performance and that their use caused little or no health risk. These data suggest that young athletes may require information regarding the limited benefits and potential risks associated with the use of ergogenic aids.

(*AJDC*. 1989;143:486-489)

Accepted for publication December 29, 1988.

From the Departments of Pediatrics (Drs Krowchuk, Anglin, Stancin, Williams, and Zimet) and Orthopaedics (Dr Goodfellow), Case Western Reserve University School of Medicine at Cleveland (Ohio) Metropolitan General Hospital.

Presented at the 28th Annual Meeting of the Ambulatory Pediatric Association, Washington, DC, May 3, 1988.

Reprint requests to Division of Adolescent Medicine, Department of Pediatrics, Cleveland Metropolitan General Hospital, 3395 Scranton Rd, Cleveland, OH 44109 (Dr Krowchuk).

Historically, athletes have used a variety of substances in an attempt to improve sports performance.[1] Agents that have been employed in this manner, collectively termed *ergogenic aids*, include anabolic steroids, stimulants (eg, amphetamines, caffeine, and related agents), and nutritional supplements (eg, protein and vitamins). Although the efficacy of various ergogenic aids remains controversial, a synthesis of existing information permits certain conclusions. Anabolic steroids appear to produce small but significant increases in body weight via increases in lean body mass.[2] In addition, athletes using these drugs may experience an increase in muscle strength beyond that achieved by weight training alone.[2] Amphetamines may also enhance athletic performance, though the increment of improvement provided is small.[3] Despite extensive research, there is no evidence that excess vitamins or protein enhances athletic performance.[1,4]

Regardless of their perceived or actual efficacy, the use of ergogenic aids may pose significant health risks for the athlete. The use of anabolic steroids, for example, may be associated with masculinization in the female; reduced sperm production, gynecomastia, and testicular atrophy in the male; and alterations in blood cholesterol levels, premature closure of the epiphyses, and hepatic cancer in both sexes.[1,2,5] Although the intake of excess vitamins or protein rarely produces adverse effects, the use of these agents represents a needless expense for the athlete.

Ergogenic aids are not uncommonly employed by professional and advanced amateur (Olympic, collegiate) athletes.[6] For example, surveys of intercollegiate athletes have estimated the prevalence of anabolic steroid use to be 15% to 20%.[7-9] Little information exists, however, regarding the use of ergogenic aids by younger athletes, and what is available centers on the use of anabolic steroids. In a study published in 1971, Toohey and Cox[10] reported that 9 (2.5%) of 361 high school athletes reported having used anabolic steroids. More recently, Johnson et al[11] found an 11.1% prevalence of use of these agents among 853 male high school students, 84% of whom were involved in sports. However, to our knowledge, no studies have addressed the prevalence of use of ergogenic aids other than anabolic steroids by high school athletes. In addition, there have been no attempts to investigate young athletes' beliefs regarding the use of these agents. The purpose of this study was to determine high school athletes'

knowledge about, attitudes toward, and past use of drugs or nutritional aids to enhance sports performance.

METHODS

Subjects for this study were student-athletes attending three suburban high schools in the greater Cleveland area who were entering grades 9 through 12, planned to take part in interscholastic sports during the 1987-1988 season, and required a preparticipation examination. The schools from which subjects were recruited competed at the AAA/Division I level, and their combined enrollment was 4678. Each school provided its athletes with advance notice of the dates and location at which sports physical examinations would be conducted. Although physical assessments were required of all athletes prior to sports participation, attendance was voluntary at either of the two sessions at which subjects were recruited. Therefore, subjects in our study represent a convenience sample of student-athletes. Preparticipation examinations were conducted in a multiple station format. Following registration but before the physical assessment process was begun, each student-athlete was given a study questionnaire, envelope, and pencil and was asked to sit at one of several widely spaced desks that assured privacy.

The study questionnaire was designed especially for this project. (A copy of the study questionnaire will be provided on request.) The questionnaire's introductory paragraph explained the purpose of the study and invited students to participate. In addition, the text advised potential subjects that taking part in the study was voluntary, that all responses would remain confidential, and that they should not write their names on the questionnaire. To ensure anonymity, athletes choosing to participate were instructed to complete the questionnaire, place it in the envelope provided, seal the envelope, and deposit it into a designated box. Athletes who did not wish to participate were instructed to place the blank questionnaire in the envelope, seal the envelope, and deposit the envelope in the same designated box.

The initial portion of the questionnaire gathered basic demographic information, including the student-athlete's age, sex, race, school, grade level, sport or sports in which he or she planned to participate, and the level at which he or she anticipated participating (varsity, junior varsity, freshman). The body of the questionnaire was designed to elicit young athletes' knowledge about, attitudes toward, and past use of certain agents to enhance sports performance.

The agents chosen for study included anabolic-androgenic steroids (referred to hereafter as anabolic steroids), amphetamines, and nutritional supplements (extra protein and vitamins). Specifically, subjects were questioned about the following: (1) their awareness of the use of these agents by athletes in an attempt to improve performance, (2) their beliefs regarding the efficacy of these agents, (3) the degree of risk they believed to be associated with the use of these agents, (4) their opinions regarding the level of competition at which the use of these agents is appropriate, (5) their perceptions of their coaches' attitudes toward the use of these agents, and (6) whether they had used or would consider using any of these agents in an attempt to enhance their own sports performance.

Table 1.—High School Athletes' Beliefs Regarding the Use of Agents to Enhance Athletic Performance

Belief	No. (%) of Athletes by Performance Agent			
	Anabolic Steroids	Amphetamines	Protein	Vitamins
Believe agent to be effective	78 (27)	28 (10)	204 (70)	174 (60)
Believe no or little risk is associated with use of agent	78 (27)	35 (12)	262 (92)	244 (87)
Believe use of agent by athletes is appropriate	74 (26)	34 (12)	213 (75)	212 (75)
Believe coach would approve of use of agent	12 (4)	5 (2)	184 (65)	179 (63)

RESULTS

Subjects for the study were recruited during two preparticipation examination sessions conducted during the summer and fall of 1987. Of 298 students attending these sessions, 295 (99%) completed questionnaires and were enrolled in the study. This sample comprised 18.4% of the 1600 participants in athletics at the three schools. It should be noted that the term *participants* is not synonymous with *student-athletes.* Since students may play more than one sport, the number of participants will be greater than the number of student-athletes. Therefore, since a significant number of our subjects (46%) played more than one sport, it is probable that our sample actually represents a somewhat larger proportion of student-athletes in these schools. The percentages presented below were calculated based on the number of subjects completing a given questionnaire item. As is common in studies employing a questionnaire, not all subjects completed all items. However, the mean completion rate for questionnaire items was 96%, with a range of 85% to 99%.

The mean age of subjects was 15.6 years, with a range of 13 to 18 years. Seventy-two percent of subjects were male, 66% were white, and 30% were black. Subjects were distributed relatively equally among the four high school grade levels. Of the athletes surveyed, 49% played one sport, 34% played two sports, and 12% played three sports. Employing the system of sports classification developed by the Committee on Sports Medicine of the American Academy of Pediatrics,[12] 56% of athletes were involved in contact sports, 11% in limited-contact sports, and 28% in noncontact sports. Among athletes participating in one or more sports, the four most commonly played sports included football (42%), basketball (19%), track or cross country (18%), and soccer (12%).

In general, young athletes were aware that certain agents may be used in an attempt to improve sports performance. One hundred forty-five respondents (55%) had heard of athletes using anabolic steroids, and 62 (25%) had heard of the use of amphetamines. One hundred forty-seven (58%) were aware of the use of protein supplements, and 143 (56%) were aware of the use of vitamins.

High school athletes' beliefs regarding the use of performance agents are presented in Table 1. Overall, young athletes expressed negative views regarding the use of anabolic steroids and amphetamines. The majority of subjects believed that anabolic steroids and amphetamines were not effective and that their use was associated with a high degree of risk. In addition, most young athletes felt that the use of these agents was not appropriate at any level of competition, and nearly all thought their

coaches would disapprove of the use of these agents. In contrast, a majority of subjects expressed positive views regarding the use of nutritional aids to enhance sports performance. The use of protein and vitamins was perceived to be both effective and safe. Overall, 75% of subjects believed that it was appropriate for athletes to use these agents, and a majority of these approved of the use of protein (83%) or vitamins (73%) at the high school level. A majority of subjects believed their coaches would approve of the use of nutritional supplements.

Only four subjects (1.4%) stated that they had taken anabolic steroids, and five subjects (1.8%) claimed that they had used amphetamines. Of related interest, a large majority of subjects reported that they would not consider the use of anabolic steroids (90%) or amphetamines (97%) in an attempt to enhance sports performance. Approximately one third of those surveyed, however, stated that they had used protein (35%) or vitamins (33%) in this capacity. Furthermore, 56% of subjects reported that they would consider the use of supplemental protein, while 52% would consider the use of extra vitamins.

We examined the relationships between student-athletes' knowledge about and attitudes toward performance drugs and the following variables: age, sex, sport played (football vs nonfootball), classification of sport played (contact, limited contact, noncontact), level of sports competition (varsity, junior varsity, freshman), and use of illicit drugs during the 12 months preceding the study. No consistent associations between student athletes' responses and age, sport played, and level of sports competition were observed. Similarly, there were no consistent associations between subjects' responses and classification of sport played, even when controlled for gender.

However, respondents' sex and past use of illicit drugs were associated with their understanding of and beliefs regarding the use of ergogenic aids. Males were significantly more likely than females to have heard of the use of anabolic steroids as a performance aid, to believe that anabolic steroids were effective, and to consider the use of anabolic steroids (Table 2). Males were also more likely to be aware of the use of nutritional supplements (protein or vitamins) as performance aids (75% vs 58%, $\chi^2 = 6.007$, $df = 1$, $P = .014$) and to have employed these agents in an attempt to improve performance (44% vs 30%, $\chi^2 = 4.197$, $df = 1$, $P = .04$). Table 3 shows that subjects who reported the use of illicit drugs during the 12 months preceding the study were more likely than nonusers to have heard of athletes' use of anabolic steroids and amphetamines to enhance performance. In addition, illicit drug users were more likely to believe that these agents were effective in improving performance (Table 3). When amphetamine use was controlled for, illicit drug users remained more likely than nonusers to be aware of the use of amphetamines and to believe in the efficacy of anabolic steroids and amphetamines.

To assess the validity of responses provided by our subjects, we compared the self-reported annual prevalence of substance use by high school seniors participating in our study with that of seniors sampled in the national survey entitled *Drug Use Among American High School Students, College Students, and Other Young Adults: National Trends Through 1985*.[13] Table 4 demonstrates that, compared with students participating in the national survey, athletes in our study reported lower annual prevalences of use of alcohol, marijuana, LSD, and cocaine. There are two competing hypotheses to account for this observation: (1) Despite our attempts at ensuring the confidentiality of responses, students taking part in our study may have underreported the use of these substances. (2) Since our sample represented a selected group of high school seniors, that is, student-athletes, the annual prevalence of use may in fact be lower than that observed nationally for the general student population. Supporting the latter hypothesis is the observation that heavy users of alcohol

Table 2.—Difference by Sex in Knowledge and Attitudes About Use of Anabolic Steroids

	No. (%) by Sex		
	Male (n = 213)	Female (n = 82)	P*
Aware of anabolic steroid use	116 (61)	32 (44)	.015
Believe anabolic steroids are efficacious	67 (32)	11 (13)	.002
Would consider using anabolic steroids	29 (14)	0 (0)	.0009

*χ^2 Statistic.

Table 3.—Awareness of Use by Athletes and Belief in Efficacy of Performance Drugs by Subjects' Use of Illicit Drugs* During Previous 12 Months

	No. (%) by Drug Use		
	Illicit Drug Users (n = 34)	Nonusers (n = 252)	P†
Aware of use of anabolic steroids	23 (74)	123 (54)	.033
Aware of use of amphetamines	14 (48)	54 (25)	.007
Belief in efficacy of anabolic steroids	14 (41)	62 (25)	.040
Belief in efficacy of amphetamines	9 (26)	19 (8)	.0005

*Marijuana, cocaine, amphetamines, LSD, and depressants.
†χ^2 Statistic.

Table 4.—Annual Prevalence* of Use of Selected Drugs by High School Seniors

	Prevalence, %	
Drug	Present Study (n = 82)	Johnston et al,[13] 1986
Alcohol	70	86
Marijuana	22	41
LSD	2	4
Cocaine	2	13

*Prevalence indicates use of the drug during the preceding 12 months.

or other chemicals are less likely than infrequent users or abstainers to be involved in organized sports.[14] Although we did not quantify the respondents' level of substance use, our subjects may be at a somewhat lower risk for this problem than high school students in general. Further study will be needed, however, to clarify this issue.

COMMENT

The present study examined high school athletes' knowledge about, attitudes toward, and past use of substances in an effort to enhance sports performance. The results of this survey disclose that a large proportion of young athletes are aware of the use of ergogenic aids. More than one half of those questioned were aware of the use of anabolic steroids, protein, and vitamins, and one fourth were aware of the use of amphetamines.

A large majority of our young athletes believed that the use of anabolic steroids and amphetamines was both ineffective and potentially harmful. In view of this, it was not surprising that only 1.4% of subjects reported the use of anabolic steroids and 1.8% reported the use of amphetamines as ergogenic aids. The low prevalence of anabolic steroid use observed among our athletes is comparable to the 2.5% prevalence reported by Toohey and Cox[10] in their survey of high school athletes but is lower than the prevalence of 11.1% observed by Johnson et al[11] in their study of male high school students, the majority of whom were involved in sports. Such apparent variation in the prevalence of anabolic steroid use may reflect actual differences in samples surveyed or underreporting of use by subjects in our study.

On initial examination, our findings might appear to offer reassurance regarding the use of anabolic steroids by high school athletes. However, our data reveal two disturbing trends. First, male athletes exhibited a somewhat more positive view of anabolic steroid use. One of every three males believed that these agents are able to improve sports performance and one in seven would consider their use. Second, subjects' use of illicit drugs in the 12 months preceding the study appeared to be associated with their awareness of and knowledge about performance aids. Specifically, users of illicit drugs were more likely than nonusers to have heard of the use of anabolic steroids and amphetamines and to believe in their efficacy. Although users and nonusers did not differ significantly when asked whether they would consider taking anabolic steroids or amphetamines, our findings suggest that users of illicit drugs may be at increased risk for the future use of these agents. Support for this hypothesis is provided by the observation of Block and Goodman[15] that illicit drug users tend to experiment with chemical agents and thus may become involved with a wide range of substances.

In contrast to their opinions regarding anabolic steroids and amphetamines, high school athletes exhibited a relatively positive view toward the use of supplemental protein or vitamins in an attempt to enhance performance. A majority of those surveyed believed these agents to be both effective and safe. One third of our athletes stated that they had used these nutritional aids, and one half stated that they would consider using such aids.

Certain limitations in our study design deserve mention. First, despite multiple efforts to ensure confidentiality, we cannot exclude the possibility that the use of ergogenic aids, particularly of illicit agents such as anabolic steroids and amphetamines, has been underreported by our subjects. Second, since ours represented an exploratory investigation, it was not possible to examine in depth the nature and magnitude of use of nutritional supplements by our subjects. Further studies will be required to address the issue of supplemental protein and vitamin use among high school athletes.

Despite these limitations, our findings indicate that young athletes harbor beliefs and attitudes that may place them at risk for using ergogenic aids. In particular, young male athletes express opinions that suggest a willingness to consider employing anabolic steroids in an attempt to enhance sports performance. In view of this, these athletes may benefit from educational interventions that address not only the limited efficacy and potential harm associated with the use of these drugs but the ethical issues involved in their use as well. Our findings also indicate that high school athletes are likely to have employed or to consider employing supplemental protein or vitamins in an attempt to improve performance. Although the intake of these substances is generally relatively safe, adverse effects may attend the use of nutritional supplements. In addition, the use of these supplements burdens an athlete and his or her family with an unnecessary expense. Therefore, young athletes may benefit from the provision of accurate information about the role of nutritional supplementation in sports performance.

We thank Michael M. Supler, LPT, and the staff of the University Suburban Sports Medicine Center, South Euclid, Ohio, for their invaluable assistance.

References

1. Dyment PG. Drug misuse by adolescent athletes. *Pediatr Clin North Am.* 1982;29:1363-1368.
2. American College of Sports Medicine. Position stand on the use of anabolic-androgenic steroids in sports. *Med Sci Sports Exerc.* 1987;19:8-12.
3. Laties VG, Weiss B. The amphetamine margin in sports. *Fed Proc.* 1981;40:2689-2692.
4. Hecker AL. Nutrition and physical performance. In: Strauss RH, ed. *Drugs and Performance in Sports.* Philadelphia, Pa: WB Saunders Co; 1987:23-52.
5. Mangi RJ, Jokel P. Drugs and sport. *Conn Med.* 1981;45:637-641.
6. Strauss RH, Curry TJ. Magic, science, and drugs. In: Strauss RH, ed. *Drugs and Performance in Sports.* Philadelphia, Pa: WB Saunders Co; 1987:3-9.
7. Toohey JV. Non-medical drug use among intercollegiate athletes at five American universities. *Bull Narc.* 1978;30:61-64.
8. Pope HG, Katz DL, Champoux R. Anabolic-androgenic steroid use among 1010 college men. *Phys Sports Med.* 1988;16:75-81.
9. Dezelsky TL, Toohey JV, Shaw RS. Nonmedical drug use behavior in five United States universities: a 15-year study. *Bull Narc.* 1985; 37:49-53.
10. Toohey JV, Cox BA. Steroids and the athlete. *Ariz J Health Phys Ed Recreat.* 1971;14:15-17.
11. Johnson MD, Jay MS, Shoup B, Rickert VI. Anabolic steroid use in adolescent males. *J Adolesc Health Care.* 1988;9:263. Abstract.
12. Committee on Sports Medicine, American Academy of Pediatrics. Recommendations for participation in competitive sports. *Pediatrics.* 1988; 81:737-739.
13. Johnston LD, O'Malley PM, Bachman JG. *Drug Use Among American High School Students, College Students, and Other Young Adults: National Trends Through 1985.* Washington, DC: US Dept of Health and Human Services; 1986. Publication ADM 86-1450.
14. Zarek D, Hawkins JD, Rogers PD. Risk factors for adolescent substance abuse. Implications for pediatric practice. *Pediatr Clin North Am.* 1987;34:481-493.
15. Block JR, Goodman N. Illicit drug use and consumption of alcohol, tobacco, and over-the-counter medicine among adolescents. *Int J Addict.* 1978;13:933-946.

Articles

Measured Energy Expenditure in Pediatric Intensive Care Patients

Samuel J. Tilden, MD; Stephanie Watkins, RRT; Timothy K. Tong, MD; Malayappa Jeevanandam, PhD

• Few data are available on energy requirements of mechanically ventilated, critically ill children. We measured the resting energy expenditure in 18 mechanically ventilated patients between ages 2 and 18 years, using indirect calorimetry. All patients had fractional inspired oxygen concentration less than 0.6, no spontaneous respirations, hemodynamic stability, and no fever or active infection, and were receiving 5% dextrose. All subjects were hypermetabolic, since the measured resting energy expenditure divided by the predicted basal energy expenditure from the Harris-Benedict equations was 1.48 ± 0.09 (mean ± SEM). The energy requirements calculated using "injury factors" and "activity factors" adapted for adults is 1.62 times basal energy expenditure. The injury factor for the pediatric multiple trauma patients should be 1.25 compared with 1.35 in adults. In these pediatric intensive care patients 33% ± 8% of the energy is derived from carbohydrates, 53% ± 8% from fat, and 14% ± 2% from protein oxidation. In individual critically ill pediatric patients, energy requirements should be estimated by measuring their resting energy expenditure whenever possible and adding 5% for their activity. In the absence of the actual measurement of resting energy expenditure, the recommended energy requirement is 1.5 times basal energy expenditure. In this acute phase of injury, the daily nitrogen requirement is 250 mg per kilogram of body weight.

(*AJDC*. 1989;143:490-492)

Nutritional support is an essential aspect of pediatric intensive care management. Its importance stems from the fact that a significant number of patients have nutritional depletion on admission or increased metabolic stress from critical illness.[1,2] Lack of appropriate nutritional support in these instances may add to the effects of disease and prolong recovery or limit survival.[3] There is a growing clinical emphasis of predicting an individual's optimum nutritional requirements.

Several studies have been undertaken in the adult population to determine the energy expenditure in critically ill patients.[2,4-9] Little, however, is known about the energy expenditure in the pediatric intensive care patient in the acute phase of injury. The purpose of this study was to determine the nutritional requirement for the critically ill pediatric patient. The technique of indirect calorimetry was used in measuring the daily resting energy expenditure (REE), and an "injury factor" was calculated by comparing REE with the predicted basal energy expenditure (BEE) in this pediatric population.

PATIENTS AND METHODS

Eighteen patients requiring mechanical ventilation in the pediatric intensive care unit were entered into the study. Informed parental consent was obtained prior to the study. The patients were studied within 72 to 96 hours of admission while they were receiving a solution of 5% dextrose accounting for between 50% and 100% of their maintenance fluid requirement. The median age was 11 years with a range of 2 to 18 years, and median weight was 33 kg with a range of 11 to 79 kg. There were 13 boys and 5 girls. Thirteen patients had accidental trauma; in most, the major injury was to the head and several had multiple injuries of lesser severity including bone fractures (Table 1). Their Injury Severity Score (ISS) ranged from 17 to 50 (mean ± SEM, 30 ± 2).

Oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and respiratory quotient (RQ) were measured between 8 and 10 AM using the metabolic cart (Horizon Metabolic Measurement Cart, Sensormedics, Anaheim, Calif). This instrument consists of a polarographic oxygen analyzer, an infrared carbon dioxide analyzer, and turbine flow meter for measuring expired volume. An air-oxygen blender (Bird Corp, Palm Springs, Calif) was used to provide a constant fractional inspired oxygen concentration to a Siemens-Servo 900C ventilator (Siemens Elema, Solna, Sweden). Sample values of inspired and expired oxygen and carbon dioxide concentrations, along with minute ventilation, were entered into a microprocessor that calculates $\dot{V}O_2$ and $\dot{V}CO_2$. The fraction of inspired oxygen varied from 0.21 to 0.55 in these studies. The metabolic measurement cart was calibrated prior to each determination using ambient air, 100% oxygen, and a known gas mixture having 24% oxygen and 8% carbon dioxide. Constancy of the measurement to test the stability of the instrument was observed for 10 to 15 minutes. Then the test measurement was performed over a 20-minute period of continuous sampling. One-minute averages of $\dot{V}O_2$ and $\dot{V}CO_2$ were printed. Each patient was resting during the study; some were sedated with diazpam or morphine sulfate. No patient received muscle relaxants within 1 hour prior to the study, and no suctioning was performed during the test. Means of $\dot{V}O_2$ and $\dot{V}CO_2$ over the 20-minute period were used to calculate REE by a modified Weir equation,[10] REE (in kilojoules per day) $= 6.02\,(3.796\dot{V}O_2 + 1.223\dot{V}CO_2) - 595UN$, where $\dot{V}O_2$ is oxygen consumption in milliliters per minute, $\dot{V}CO_2$ is carbon dioxide production in milliliters per minute, and UN is urinary nitrogen excretion in millimoles per day. In the absence of urinary nitrogen data, the following formula was used: REE (in kilojoules per day) $= 6.02(3.796\dot{V}O_2 + 1.214\dot{V}CO_2)$.

In 11 patients, 24-hour urine was collected through a Foley catheter, and the urinary total nitrogen excretion value was determined by a chemiluminescence technique (Chemiluminescence Digital Nitrogen Analyzer, Antek Co, Houston, Tex). Predicted BEE was obtained from each subject's height, age, weight, and sex using the appropriate Harris-Benedict equations.[11] The degree of hypermetabolism was calculated by dividing REE by BEE. Whenever urinary nitrogen excretion values were known, the

Accepted for publication December 26, 1988.

From Pediatric Intensive Care Unit, Children's Health Center, and Trauma Center, St Joseph's Hospital and Medical Center, Phoenix, Ariz.

Reprint requests to PICU, Children's Hospital, 1600 7th Ave S, Birmingham, AL 35233 (Dr Tilden).

Table 1.—Clinical Diagnoses of Study Patients

Type of Diagnosis	No. of Patients
Trauma	
Closed head injury	4
Closed head injury with craniotomy	4
Closed head injury with long-bone fracture	3
Closed head injury with exploratory laparotomy	1
Quadriplegia	1
Other	
Laparotomy and colon resection	2
Brain tumor resection	1
Guillain-Barré	1
Near drowning	1
Total	**18**

Table 2.—Clinical Data of Study Patients*

	Mean ± SEM	Range
Age, y	10 ± 1	2-18
Body weight, kg	40 ± 5	11-79
Height, cm	142 ± 6	86-183
Body surface area, m^2	1.23 ± 0.11	0.51-1.94
ISS†	29.9 ± 2.4	17-50
BEE, kJ/d	4830 ± 462	2016-8232
REE,		
kJ/d	6711 ± 592	3628-10 690
kJ/kg/d	194 ± 16	130-336
$kJ/m^2/d$	5724 ± 327	3851-8379
% BEE	148 ± 9	100-228
RQ	0.83 ± 0.02	0.65-0.96
$\dot{V}O_2$		
mL/min	229 ± 20	121-394
$mL/min/m^2$	192 ± 11	132-304
Nitrogen excretion,†		
mmol/d	570 ± 90	210-1070
mmol/kg/d	15.6 ± 2.57	3.07-27
Fat oxidation,† % REE	52.9 ± 8.2	...
Carbohydrate oxidation,† % REE	33.5 ± 7.8	...
Protein oxidation,† % REE	13.6 ± 2.1	...

*Data are expressed for 18 patients unless otherwise indicated. ISS indicates Injury Severity Score; BEE, basal energy expenditure; REE, resting energy expenditure; RQ, respiratory quotient; and Vo_2, oxygen consumption.

†Data are expressed for 11 patients.

nonprotein RQ and the net substrate (fat, carbohydrate, and protein) oxidation rates were calculated using the Weir formula[10] modified by Frayn.[12]

Since a wide range of pediatric patients were included in the study, the data for REE were normalized to body weight, body surface area, or BEE. All results were expressed as means ± SEMs. Correlation between measured REE and predicted BEE values was determined using linear regression analysis. $P \leq .05$ was considered statistically significant.

RESULTS

The diagnostic categories of patients studied are given in Table 1, and the clinical data are summarized in Table 2. The study population was heavily weighted by patients with severe trauma or who required surgical procedures. The patients were hypermetabolic as shown by the high (1.48 ± 0.09) ratio of REE to BEE. They were also severely catabolic, with a daily urinary nitrogen loss of 15.63 ± 2.57 mmol/kg per day, which is comparable (17.06 mmol/kg per day) with equally injured (ISS, 27.4 ± 2.2; REE to BEE ratio, 1.52 ± 0.06) adult (age, 38 ± 5 years) trauma intensive care patients.[13] There was a significant correlation ($r = .88$; $P = .001$) between measured REE and predicted BEE. This relationship in the pediatric patients is shown in the Figure. Similar correlations ($r = .83$, $P = .001$) were also seen in normal healthy adults,[14] demonstrating the general applicability of the BEE, irrespective of age or injured state.

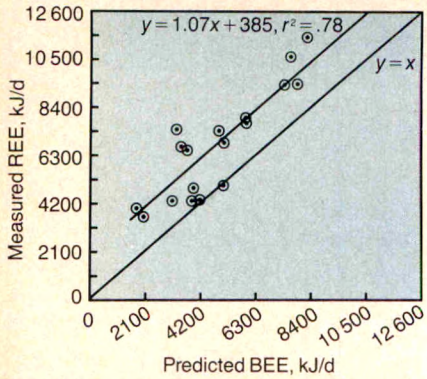
Total RQ of 0.83 ± 0.02 indicated a mixed substrate utilization, predominantly from fat sources. The measurement of 24-hour urinary total nitrogen enabled us to calculate the nonprotein RQ and, hence, the net substrate oxidation rates. During this study, the patients received only 5% dextrose infusion and no nitrogen. Hence, the relative energy contributions of fat, carbohydrates, and protein (53%, 33%, and 14%, respectively) oxidation to the REE is a reliable one for arriving at the optimal nutritional support mixture for the pediatric patients in the immediate recovery phase.

There is a weak (but significant) correlation ($r = .56$) between daily nitrogen excretion and energy expenditure both normalized to body weight. We could not find any correlation of the different parameters with ISS and this, perhaps, may be due to the high ISS (ISS, 25) given to the head trauma alone when our mean ISS was 29.9 ± 2.4.

COMMENT

This study suggests that critically ill, mechanically ventilated pediatric patients have increased energy requirements. The measured REE averaged 48% more than predicted BEE from the Harris-Benedict equations. Although to our knowledge no previous studies address the specific issue of measured energy expenditure in mechanically ventilated children, one previous report of adolescent head injury victims found a 30% increase in measured REE compared with predicted BEE by the Harris-Benedict equations.[15] The patients were fed in their study, and only the mean value over a 14-day period was reported. Measured REE correlated well with predicted BEE from Harris-Benedict equations. The correlation for pediatric patients was similar to that seen in normal adults.[14]

Winthrop et al[16] measured energy expenditure in 19 children after blunt trauma. They found a 14% increase in measured energy expenditure over basal metabolic rate. Also, their data suggested that measured REE increased with increased severity of injury but no correlation existed between ISS and any of the parameters of protein metabolism. None of their patients, however, required mechanical ventilation. The higher measured energy expenditure in our study may have been due to a greater severity of illness in our patients, all of whom required mechanical ventilation.



Linear relationship between the predicted (by Harris-Benedict equation) and measured resting energy expenditure (REE). BEE indicates basal energy expenditure.

There was a large variation in measured REE among our study patients (range, 3630 to 10 690 kJ). This may have partly been due to the wide spectrum of age group (2 to 18 years) included and was narrowed when REE was calculated as a function of body weight or body surface area (Table 2) and limited the application of prediction equations to accurately predict energy expenditure in individual patients.

The "activity" and "injury factors" are mathematical corrections to account for increased energy requirements due to physical activity, disease, or injury.[2,17] In the clinical setting, the daily energy requirements are calculated by adding the increased energy represented by the above stress factors to the BEE. The most commonly used estimate of BEE requirements are based on the Harris-Benedict equations,[10] which took into consideration age, sex, weight, and height. Although they were originally developed for an adult population, the authors also applied them to data for children. Long et al[2] had developed for adult patients activity factors and injury factors. When these factors for confinement to bed (1.20) and skeletal trauma (1.35) were considered for our pediatric patients, then BEE calculated from the Harris-Benedict equations should have been multiplied by 1.62 to get the REE, but actually it was only 1.48. If the injury factors for pediatric patients were revised to 1.25, then BEE × 1.50 = REE. Hence, for the pediatric patients with skeletal trauma, the energy requirements could be calculated by multiplying predicted BEE by a combined factor of 1.50. This was helpful in clinical situations where indirect calorimetry measurements were not available.

This study demonstrated that energy expenditures could be measured safely in critically ill pediatric patients. There were no complications associated with the use of the metabolic measurement cart. Air leak around the endotracheal tube was not a problem in this study. Lack of an air leak was confirmed on clinical examination by absence of an audible air leak during mechanical inspiration and during testing by the presence of stable minute-to-minute RQ values. Measurements of substrate utilization by indirect calorimetry offers a means of matching nutritional therapy to individual patient needs. In critically ill, mechanically ventilated, pediatric patients in hemodynamically stable condition, about half of the energy comes from the fat fuel source and one third from the oxidation of carbohydrates. In providing nonprotein energy to the pediatric trauma patients, equal partitioning of lipid and carbohydrate energy could be recommended. The nitrogen excretion data lead to a provision of 250 mg of nitrogen per kilogram of body weight per day for approaching nitrogen equilibrium. Thus, in the nutritional management of the pediatric trauma patients, during the early phase of injury, the following prescription could be followed:

Energy requirement is 1.50 times BEE or measured REE plus 5% for activity energy expenditure[8]; nonprotein energy equally divided between lipid and carbohydrate sources; and balanced amino acids, 250 mg of nitrogen per kilogram of body weight per day with necessary vitamins, electrolytes, and trace minerals.

Since pediatric patients' requirements change with resolution of trauma response, the above prescription should be altered by keeping a close watch on weight change, clinical improvement, or complications and metabolic alterations.

This study confirms that critically ill, mechanically ventilated pediatric patients, as a group, have greatly increased energy expenditure compared with predicted values. Measurement of energy expenditure is desirable and may be accomplished in children weighing more than 11 kg by use of commercially available equipment. Bedside indirect calorimetry provides an improved index for nutritional assessment in critically ill pediatric patients.

We thank William R. Schiller, MD, for fostering our interest in this problem, and Russell Cunningham, MD, for his helpful suggestions with the manuscript. We also wish to thank Carol Krienick for statistical assistance, and Diana Getz for her secretarial support.

References

1. Pollack MM, Rittiman UE, Wiley JS. Nutritional depletion in critically ill children: associations with physiologic instability and increased quantity of care. *JPEN*. 1985;9:309-313.
2. Long CL, Schaffel N, Geiger JW, Schiller WR, Blakemore WS. Metabolic response to injury and illness: estimation of energy and protein needs from indirect calorimetry and nitrogen balance. *JPEN*. 1979;3:452-456.
3. Moyer E, Cerra F, Chenier R, et al. Multiple systems organ failure, VI: death predictions in the trauma-septic state—the most critical determinants. *J Trauma*. 1981;21:862-869.
4. Damesk MC, Schwarz Y, Weissman C. Energy measurements and requirements of critically ill patients. *Crit Care Clin*. 1987;3:71-96.
5. Askanazi J, Carpentier YA, Elwyn DH, et al. Influence of total parenteral nutrition on fuel utilization in injury and sepsis. *Ann Surg*. 1980;191:40-46.
6. Swinamer DL, Phang PT, Jones RL, Grace M, King EG. Twenty-four hour energy expenditure in critically ill patients. *Crit Care Med*. 1987;15:637-643.
7. Bartlett RH, Dechert RE, Mault JR, Ferguson SK, Kaiser AM, Erlandson EE. Measurement of metabolism in multiple organ system failure. *Surgery*. 1982;92:771-778.
8. Weissman C, Kemper M, Askanazi J, Hyman AI, Kinney JM. Resting metabolic rate of the critically ill patient: measured versus predicted. *Anesthesiology*. 1986;64:673-679.
9. Wilmore DW. Nutrition and metabolism following thermal injury. *Clin Plast Surg*. 1974;1:603-615.
10. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. *J Physiol*. 1949;109:1-9.
11. Harris JA, Benedict FG. *Biometric Studies of Basal Metabolism in Man*. Washington, DC: Carnegie Institute; 1919. Publication 279.
12. Frayn KN. Calculation of substrate oxidation rates in vivo from gaseous exchange. *J Appl Physiol*. 1983;55:628-634.
13. Jeevanandam M, Young DH, Ramias L, Schiller WR. Aminoaciduria of severe trauma. *Am J Clin Nutr*. 1989;43:814-822.
14. Daly JM, Heymsfield SB, Head CA, et al. Human energy requirements: overestimation by widely used prediction equation. *Am J Clin Nutr*. 1985;42:1170-1174.
15. Phillips R, Ott L, Young B, Walsh J. Nutrition support and measured energy expenditure of the child and adolescent with head injury. *J Neurosurg*. 1987;67:846-851.
16. Winthrop AL, Wesson DE, Pencharz PB, Jacobs DG, Tibor H, Filler RM. Injury severity, whole-body protein turnover, and energy expenditure in pediatric trauma. *J Pediatr Surg*. 1987;22:534-537.
17. Wilmore DW. *The Metabolic Management of the Critically Ill*. New York, NY: Plenum Publishing Corp; 1977:5-31.

Frequency of Autoantibodies in Normal Children

Alberto Martini, MD; Renata Lorini, MD; Domenico Zanaboni; Angelo Ravelli, MD; Roberto G. Burgio, MD

• Very few data have been reported on the frequency of autoantibodies (AAs) in normal children. In the present study we investigated the frequency of 14 AAs in a total of 268 apparently normal children (151 boys and 117 girls; age range, 1 month to 14 years). Forty-one children (22 boys and 19 girls) were positive for at least one AA, usually in a low titer; two children were positive for two AAs. None of these children had a personal or family history of autoimmune diseases. The percentage of children positive for each AA was as follows: antinuclear, 3%; anti–smooth muscle, 2.6%; antireticulin, 2.6%; antimitochondrial, 1.1%; rheumatoid factor, 0.6%; antiribosomal, 0.4%; anti–gastric parietal cells, 5.2%; and anti–thyroid microsomal, 1.3%. Anti–double-stranded DNA, anti–intestinal epithelial cells, anti-liver and antikidney microsomal, antithyroglobulin, anti–islet cells, and complement-fixing anti–islet cell antibodies were not detected in any serum. Fifteen of the 41 positive children were checked for the presence of AAs two years later; six (40%) were still positive, always for the same AA, without major differences in titer. Our results suggest that the overall frequency of AAs in apparently healthy children is quite similar to that reported in young adults; this AA positivity seems most often to represent a transient phenomenon.

(*AJDC* 1989;143:493-496)

The frequency of serum autoantibodies (AAs) in normal children is not well established; very few reports have been devoted to this subject[1-4] and a limited number of AAs usually have been studied. Moreover, it is not known whether or not AA positivity in apparently normal children represents a transient phenomenon. In the present study we investigated the frequency of 14 serum AAs in a total of 268 apparently healthy children. Fifteen of 41 children found positive for the presence of AAs were checked again two years later.

SUBJECTS AND METHODS

Subjects

A total of 268 apparently healthy children (age range, 1 month to 14 years; mean age, 6.9 years; 151 boys and 117 girls) were studied. Extra blood was obtained with the parents' permission at the time of routine venipuncture in 129 children during a community health study and in 139 children during hospitalization for simple surgical procedures. All of the children were in apparently good health and none presented evidence of infectious or autoimmune diseases. Parents of the children who were found to be positive were notified about the results, their clinical significance, and the possibility of controlling the AA positivity two years later. Serum was stored at −20°C until tested.

Serologic Techniques

Fourteen AAs (seven non–organ-specific and seven organ-specific) were studied.

Non–Organ-Specific Antibodies.—Rheumatoid factor was determined by a latex agglutination test (Reuma Test, Sclavo Diagnostic, Italy) using serum diluted 1:20. All of the other non–organ-specific AAs were detected by indirect immunofluorescence; serum was diluted 1:10 except for antinuclear antibody, which was diluted 1:20. Rat liver and kidney cryostat sections were used as substrates for antinuclear, antimitochondrial, antiribosomal, anti–smooth muscle (SMA), and antireticulin antibodies; anti–double-stranded DNA antibodies were detected using a *Crithidia luciliae* assay (Kallestad Laboratories, Texas).

Organ-Specific Antibodies.—Antibodies to thyroglobulin and thyroid microsomal antigens were detected by passive hemagglutination using Wellcome (Wellcome Diagnostic, England) "Thymune" kits; the lowest serum dilution considered positive was 1:20 for thyroglobulin antigen and 1:100 for thyroid microsomal antigen. All other organ-specific AAs were detected on cryostatic sections by indirect immunoflorescence; serum was tested undiluted except for anti–gastric parietal cell antibodies, with which a dilution of 1:10 was employed. Normal human stomach was used for the determination of anti–gastric parietal cell antibodies, normal human duodenum was used for anti–intestinal epithelial cell antibodies, and rat liver and kidney were used for anti–liver/kidney microsomal antibodies; islet cell antibodies (ICA-IgG) and complement-fixing ICA (CF-ICA) were determined on normal human group 0 pancreas.

Fluorescence isothiocyanate–conjugated rabbit anti–human IgA, IgG, and IgM, and antiserum (Dakopatts, Denmark) were used in indirect immunofluorescence assays at a working dilution of 1:50. Fluorescence was recorded independently by two observers using a Zeiss photomicroscope III (Carl Zeiss, West Germany) equipped with a 50-W mercury vapor lamp: the intensity of staining was graded as negative (−), weakly positive (+), positive (++), and strongly positive (+++). For antinuclear antibody and rheumatoid factor, titration of positive serum was performed. For each AA a serum of known positivity for that AA was used as control. Searches for rheumatoid factor, thyroglobulin, thyroid microsomal antigens, ICA-IgG, and CF-ICA were not carried out in all 268 subjects.

Statistical Analysis

The χ^2 test with Yates' correction, when appropriate, was used for analysis of the data.

RESULTS

The results for non–organ-specific AAs are summarized in Table 1 and results for organ-specific AAs are summarized in Table 2. Forty-one children (19 girls and 22 boys) were positive for at least one AA; two were positive for more than one AA (antinuclear antibody and SMA in one case and SMA and gastric parietal cell antibodies in the other case). The degree of antinuclear antibody positivity was usually low (Tables 1 and 2). The pattern of positivity for antinuclear antibody was speckled in

Accepted for publication Sept 30, 1988.

From the Department of Pediatrics, University of Pavia, Italy.

Presented in part at the VIII EULAR Workshop for Rheumatology Research, Corfu, Greece, March 18, 1988.

Reprint requests to Dipartimento di Pediatria, Università di Pavia, Policlinico S Matteo, 27100 Pavia, Italy (Dr Martini).

Table 1.—Incidence of Non–Organ-Specific Autoantibodies in Normal Children of Various Ages*

Age Group, y	No. of Subjects Positive/No. of Subjects Tested (% Positive)						
	ANA	ds-DNA	AMA	RA	SMA	ARA	RF
0-4	2/78 (2.6)	0/78 (0)	1/78 (1.3)	1/78 (1.3)	2/78 (2.6)	2/78 (2.6)	0/52 (0)
5-9	2/112 (1.8)	0/112 (0)	0/112 (0)	0/112 (0)	3/112 (2.7)	3/112 (2.7)	0/71 (0)
10-14	4/78 (5.1)	0/78 (0)	2/78 (2.6)	0/78 (0)	2/78 (2.6)	2/78 (2.6)	1/45 (2.2)
0-14	**8/268** (3.0)	**0/268** (0)	**3/268** (1.1)	**1/268** (0.4)	**7/268** (2.6)	**7/268** (2.6)	**1/168** (0.6)

*ANA indicates antinuclear antibody; ds-DNA, double-stranded DNA antibody; AMA, antimitochondrial antibody; RA, antiribosomal antibody; SMA, anti–smooth muscle antibody; ARA, antireticulin antibody; and RF, rheumatoid factor. The degree of autoantibody positivity or titer is as follows (the number of subjects positive is in parentheses): ANA = 1/20 (5), 1/40 (3); AMA = + (3); RA = + (1); SMA = + (7); ARA = + (4), + + (3); RF = 1/20 (1).

Table 2.—Incidence of Organ-Specific Autoantibodies in Normal Children of Various Ages*

Age Group, y	No. of Subjects Positive/No. of Subjects Tested (% Positive)						
	PCA	IECA	TgA	MsA	ICA-IgG	CF-ICA	LKM
0-4	2/78 (2.6)	0/78 (0)	0/35 (0)	0/35 (0)	0/27 (0)	0/27 (0)	0/78 (0)
5-9	5/112 (4.5)	0/112 (0)	0/68 (0)	0/68 (0)	0/21 (0)	0/21 (0)	0/112 (0)
10-14	7/78 (9.0)	0/78 (0)	0/51 (0)	2/51 (3.9)	0/33 (0)	0/33 (0)	0/78 (0)
0-14	**14/268** (5.2)	**0/268** (0)	**0/154** (0)	**2/154** (1.3)	**0/81** (0)	**0/81** (0)	**0/268** (0)

*PCA indicates anti–gastric parietal cell antibody; IECA, anti–intestinal epithelial cell antibody; TgA, antithyroglobulin antibody; MsA, antithyroid microsomal antibody; ICA-IgG, anti–islet cell immunoglobulin; CF-ICA, complement-fixing anti–islet cell antibody; and LKM, anti–liver and kidney microsomal antibody. The degree of autoantibody positivity or titer is as follows (the number of positive subjects is in parentheses): PCA = + (9), + + (5); MsA = 1/100 (1), 1/1600 (1).

five cases and homogeneous in three cases. The type of antireticulin antibody[5] was R1 in four serum samples, R2 in one sample, and R1 and R2 in two samples. The pattern of SMA[6] was SMAV (vessels) in six specimens and SMAG (glomeruli) in one specimen. For each AA no significant differences were found between sexes or among the different age groups. However, when the total number of positive subjects in each age group was considered, the older children (10 to 14 years of age) presented a significantly higher incidence of AAs than the other age groups taken either separately ($P<.05$) or as a whole (0 to 9 years of age) ($P<.01$). Maternal antibodies still circulating in the children did not contribute to the positivity for AAs observed in the youngest age group (0 to 5 years) since we did not find AAs in children younger than 6 months of age.

Anti–double-stranded DNA antibodies, intestinal epithelial cell antibodies, liver/kidney microsomal antibodies, thyroglobulin, ICA, and CF-ICA were not detected in any serum specimen.

Fifteen of the 41 children who tested positively were checked for the presence of AAs two years later (Table 3). None of them had a personal or family history of autoimmune diseases. Six children (40%) were still positive, always for the same antibody, without major differences in AA titers.

Table 3.—Results Obtained After Two Years in 15 Positive Subjects

Autoantibody*	No. of Subjects		
	Tested	Positive	Negative
ARA	4	2	2
PCA	4	0	4
ANA	2	2	0
SMA	3	2	1
AMA	1	0	1
RA	1	0	1
Total	**15**	**6**	**9**

*ARA indicates antireticulin antibody; PCA, anti–gastric parietal cell antibody; ANA, antinuclear antibody; SMA, anti–smooth muscle antibody; AMA, antimitochondrial antibody; and RA, antiribosomal antibody.

COMMENT

We determined the frequency of 14 AAs in a total of 268 apparently healthy children and found that 41 were positive for at least one AA. Considering that five of the 14 AAs were not investigated in all 268 children, the percentage of positive cases is 16.1%.

To our knowledge, the only study similar to ours with respect to the number of AAs and the number of children investigated is that by Goel et al[2]; they found a much higher frequency of positive serum (29.1%) in their study of nine serum AAs in 112 children and 22 young adults attending hospitals because of minor trauma or for simple surgical procedures. The reasons for this discrepancy probably depend mainly on differences among the commercial preparations used to perform the test. It is interesting to note, however, that Hooper et al[7] found 21.6% positive subjects in a study of six AAs in 3492 normal adults 21 to 94 years of age; moreover, Hooper et al[7] confirmed the finding[8] that in adults the overall prevalence of AAs increased steadily with age, with a steep increase in very old subjects. If we compare the results obtained for the

five AAs (antinuclear antibody, rheumatoid factor, SMA, parietal cell antibody, and thyroid microsomal antigen) that were investigated in all three studies and if, with regard to Hooper and colleagues'[7] study, we consider only the data pertaining to 551 young adults 21 to 30 years of age, the respective frequency of positive cases is 24.6% (Goel et al[2]), 10.8% (Hooper et al[7]), and 12% (present study). As previously mentioned, in adults the prevalence of AAs rises steadily with age and our results also showed a significantly higher frequency of AAs in older children; the percentage of positive serum in children would therefore probably not be expected to exceed that observed in young adults; thus, our results are probably closer to the true frequency of AAs in normal children than are the results reported by Goel et al.[2]

Two (4.9%) of 41 serum samples were positive for more than one AA; Hooper et al[7] found a much higher percentage (16.7%) of serum positive for more than one AA in adults studied for a smaller number of AAs. In our positive subjects the AA titer or intensity of staining were usually low. No significant differences in the female-male ratio were observed; this is different from what has been described in adults, in whom positive cases were reported more frequently in women (27.5%) than in men (13.7%).[7]

Fifteen of the 41 positive children were checked again two years later. Only six (40%) were still positive, always for the same AA, without major differences in AA titers.

Some additional considerations can be made with regard to the various AAs studied. Circulating antinuclear antibodies occur during some infectious disorders and in different percentages in most connective tissue diseases.[9] Eight serum specimens (3%) were antinuclear antibody–positive in low titers and usually had a speckled pattern. Exactly the same frequency has been reported by Petty et al[1] in 90 normal children, while Goel and colleagues[2] failed to find positive serum among the 112 children they studied. The percentage in the present study is similar to the 2.1% reported in adults 21 to 70 years of age, while a higher frequency (5.4%) has been found in adults over 70 years of age.[7] With the exception of very old subjects, the frequency of antinuclear antibodies in apparently normal individuals therefore seems to be similar in children and adults. Circulating antireticulin antibodies are most frequently found in celiac disease and dermatitis herpetiformis, but may be also found in other diseases.[5] At least two different fibrillary antibodies demonstrable by immunofluorescence, R1 and R2, exist in human serum. In the present study seven children (2.6%) were positive: four for R1, one for R2, and two for both R1 and R2. Kokkonen and coworkers[4] found positivity of 5.1% in children, and Hooper et al[7] found positivity of 4% in adults. It has been recently reported that the presence of IgA-class R1 antireticulin antibody is a sensitive and specific indicator of coeliac disease[10]; we do not know the Ig class of the R1 antireticulin antibody observed in our children, since in the present study we did not use Ig class-specific antiserum.

Circulating SMAs occur most often in patients with chronic hepatitis, but they have also been demonstrated in some malignant diseases and in viral infections.[6] Three distinct immunofluorescence patterns based on the appearances in rat kidney have been defined: SMAV (vessels), when serum stains the vessel walls exclusively; SMAG (glomeruli), when both vessels and glomeruli are positive; and SMAT (tubular), when vessels, glomeruli, and tubular basement membrane are stained. Seven serum specimens (2.6%) were positive in our study, six with an SMAV pattern and one with an SMAG pattern. Similar[2,11] or higher[4] percentages have been previously reported in children. It should be noted, however, that the frequency of SMAs in normal adults has been reported to range from 1.5% to 20%[11]; this great variability is probably due to the fact that low titers of SMAs may be found as a transient phenomenon in up to 80% of patients with viral infections.[6] Two of the three children who were positive were, however, still positive when checked again two years later.

Circulating antimitochondrial antibodies represent a heterogeneous group of AAs that have been reported in primary biliary cirrhosis as well as in other liver diseases, connective tissue diseases, and other miscellaneous conditions.[12] Three (1.1%) of our subjects were positive for antimitochondrial antibody. Percentages varying from 0%[2] to 1%[4] have been previously reported in children.

One child (0.4%) was positive for ribosomal antibody; this AA, detected by immunofluorescence on various tissues, including stomach, has been reported to occur in less than 1% of patients with systemic lupus erythematosus.[13] This child was no longer positive two years later. The finding of ribosomal antibody in normal children may cast doubts about its importance in such a low percentage of patients with systemic lupus erythematosus.

Circulating rheumatoid factor is associated most directly with seropositive polyarticular juvenile rheumatoid arthritis, but may be found in other connective tissue diseases as well as in diseases in which hypergammaglobulinemia occurs.[9] Only one (0.6%) of our 160 subjects tested was positive; Goel et al[2] found positive cases among 1.5% of children and Hooper et al[7] found a 2.8% positive rate in adults.

Fourteen (5.2%) children were positive for parietal cell antibodies, an AA occurring very frequently in patients with pernicious anemia.[14] Percentages varying from 1.7% to 8.9% have been previously reported in children.[2-4,15] Hooper and colleagues[7] found a similar percentage of positivity (4.8%) in adults. None of the four children whom we checked again two years later was positive, suggesting that parietal cell antibody positivity in childhood is a transient phenomenon. Circulating thyroglobulin antibodies or thyroid microsomal antigens are found in chronic thyroiditis and other thyroid or endocrine disorders, as well as in other conditions.[16] None of our subjects was positive for thyroglobulin antibodies, while two were positive for thyroid microsomal antigens (1.3%). The percentages previously reported in children vary from 0% to 4.1% for thyroglobulin antibodies and from 3.1% and 10% for thyroid microsomal antibodies,[2,4,15] depending on the serologic techniques employed. Anti–double-stranded DNA antibodies in substantial titers are considered to be highly suggestive of SLE[9]; antiliver and antikidney microsomal

antibodies have been described in a subgroup of patients, including children with chronic active hepatitis[17,18]; anti–intestinal epithelial cell antibodies have been reported in association with atrophy of the intestinal mucosa[19]; anti–islet cell antibodies and complement-fixing anti-ICA are found in the early stages of insulin-dependent diabetes mellitus.[20] None of these AAs were detected in our subjects.

Our results suggest that the overall frequency of AAs in apparently healthy children is lower than has been previously reported and is similar to that observed in young adults. We observed a significantly higher frequency of AAs in older children but, despite what has been reported in adults, the frequency of the various AAs did not differ significantly between sexes; moreover, the percentage of children positive for more than one AA was much lower than that reported in adults. The titer of AA was usually low, and when positive children were checked again two years later, only 40% were still positive. These findings suggest that AA positivity in apparently normal children is more often a transient phenomenon. Follow-up studies and determination of AA characteristics (isotype, affinity, idiotype restriction) could be helpful in establishing the possible importance of the persistence of low titers of AAs in the serum of some children.

References

1. Petty RE, Cassidy JT, Sullivan DB: Clinical correlates of antinuclear antibodies in juvenile rheumatoid arthritis. *J Pediatr* 1973;83:386-389.
2. Goel KM, Shanks RA, Whaley K, et al: Autoantibodies in childhood connective tissue diseases and in normal children. *Arch Dis Child* 1975;50:419-423.
3. Bright GM, Blizzard RM, Kaiser DL, et al: Organ-specific autoantibodies in children with common endocrine diseases. *J Pediatr* 1982;100:8-14.
4. Kokkonen J, Kiuttu J, Mustonen A, et al: Organ-specific antibodies in healthy and diabetic children and young adults. *Acta Paediatr Scand* 1982;71:223-226.
5. Rizzetto M, Doniach D: Types of 'reticulin' antibodies detected in human sera by immunofluorescence. *J Clin Pathol* 1973;26:841-851.
6. Bottazzo GF, Florin-Christensen A, Fairfax A, et al: Classification of smooth muscle autoantibodies detected by immunofluorescence. *J Clin Pathol* 1976;29:403-410.
7. Hooper B, Whittingham S, Mathews JD, et al: Autoimmunity in a rural community. *Clin Exp Immunol* 1972;12:79-87.
8. Svec KH, Veit BC: Age-related antinuclear factors: Immunologic characteristic and associated clinical aspects. *Arthritis Rheum* 1967;10:509-516.
9. Cassidy JT: *Textbook of Pediatric Rheumatology.* New York, John Wiley & Sons Inc, 1982.
10. Maki M, Hallstrom O, Vesikari T, et al: Evaluation of a serum IgA-class reticulin antibody test for the detection of childhood celiac disease. *J Pediatr* 1984;105:901-905.
11. Andersen P: Correlation of smooth-muscle and antinuclear antibodies in normal subjects. *Clin Exp Immunol* 1977;27:74-77.
12. Meek F, Khoury EL, Doniach D, et al: Mitochondrial antibodies in chronic liver diseases and connective tissue disorders: Further characterization of the autoantigens. *Clin Exp Immunol* 1980;41:43-54.
13. Homberg JC, Rizzetto M, Doniach D: Ribosomal antibodies detected by immunofluorescence in systemic lupus erythematosus and other collagenoses. *Clin Exp Immunol* 1974;17:617-628.
14. Bernhardt H, Burkitt LL, Fields ML, et al: The diagnostic significance of the parietal cell immunofluorescent test. *Ann Intern Med* 1965; 63:635-641.
15. Riley WJ, Maclaren NK, Lezotte DC, et al: Thyroid autoimmunity in insulin-dependent diabetes mellitus: The case for routine screening. *J Pediatr* 1981;98:350-354.
16. Bigazzi PE, Rose NR: Tests for antibodies to tissue-specific antigens, in Rose NR, Friedman H (eds): *Manual of Clinical Immunology.* Washington, DC, American Society for Microbiology, 1976, pp 682-691.
17. Smith MGM, Williams R, Walker G, et al: Hepatic disorders associated with liver/kidney microsomal antibodies. *Br Med J* 1974;2:80-84.
18. Maggiore G, Bernard O, Homberg JC, et al: Liver disease associated with anti-liver-kidney microsome antibody in children. *J Pediatr* 1986; 108:399-404.
19. Martini A, Scotta MS, Notarangelo LD, et al: Membranous glomerulopathy and chronic small-intestine enteropathy associated with autoantibodies directed against renal tubular basement membrane and the cytoplasm of intestinal epithelial cells. *Acta Paediatr Scand* 1983;72:931-934.
20. Bottazzo GF, Dean BM, Gorsuch AN, et al: Complement fixing islet-cell antibodies in type-I diabetes: Possible monitors of active beta-cell damage. *Lancet* 1980;1:668-672.

In Other AMA Journals

ARCHIVES OF OPHTHALMOLOGY

Visual, Refractive, and Keratometric Results of Epikeratophakia in Children: A Two-Year Follow-up
Risto J. Uusitalo, MD, Juha Lehtosalo, MD (*Arch Ophthalmol.* 1989;107:358-363)

Acute Comitant Estropia in Children With Brain Tumors
A. Sydney Williams, MD, Creig S. Hoyt, MD (*Arch Ophthalmol.* 1989;107:376-378)

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Screening for Hepatitis Infectivity Among Blood Donors: A Model for Blood Safety?
Roger Y. Dodd, PhD (*Arch Pathol Lab Med.* 1989;113:227-231)

The Duty to Warn About Transfusion Risks
David E. Willett, JD (*Arch Pathol Lab Med.* 1989;113:307-310)

When their recipe calls for allergy relief the twins take Tavist® Syrup

Tavist® Syrup contains the right ingredient to relieve allergies and keep the twins in the kitchen. One dose provides up to 12 hours of effective relief from symptoms of allergic rhinitis and mild urticaria.

Tavist® Syrup also has a convenient b.i.d. dosage to aid compliance, and a pleasant citrus taste even these master chefs can appreciate.

Prescribe the liquid allergy medicine that Pediatricians prescribe more than any other.* Prescribe Tavist® Syrup.

Tavist® Syrup. Lets kids be kids 12 hours long

(clemastine fumarate) 0.67mg/5ml

© 1989 Sandoz Pharmaceuticals Corporation

*National Prescription Audit, IMS America, LTD. Data on file, Sandoz Pharmaceuticals Corporation

Please see following page for brief summary of prescribing information.

TAS-489-2

BRIEF SUMMARY

TAVIST®

(clemastine fumarate) SYRUP 0.5 mg/5 ml
(present as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

Tavist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see *DOSAGE AND ADMINISTRATION*).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see *PRECAUTIONS — Drug Interactions* in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see *PRECAUTIONS — Nursing Mothers* in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist® (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (6 mg clemastine).

For Urticaria and Angioedema — The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED

Tavist® (clemastine fumarate) Syrup

Clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

[TAS-Z3 APRIL 1, 1986]

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

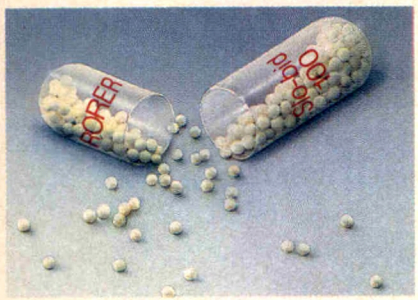
Don't Forget!

Send for the latest edition of the free Consumer Information Catalog. ☐ The Catalog lists over 200 selected federal publications of consumer interest on subjects like health, nutrition, federal benefits, money management. ☐ The Catalog is free and so are many of the booklets. ☐ Just send your name and address, no strings attached. Write today:

Consumer Information Center
Department DF
Pueblo, Colorado 81009

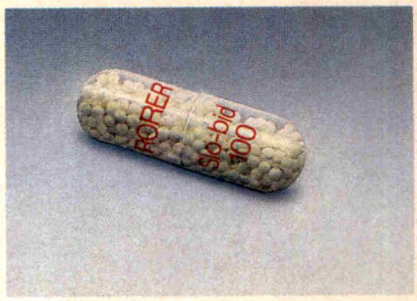
A public service of this publication and the Consumer Information Center of the U.S. General Services Administration.

Growing up on a steady theophylline is an open-and-shut case



Sprinkled

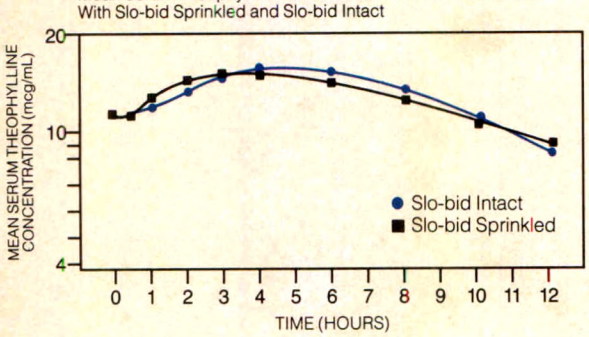
Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration[1]

Mean Serum Theophylline Concentration in 14 Children Dosed With Slo-bid Sprinkled and Slo-bid Intact



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.[2]

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in applesauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

In asthma and bronchitis

Slo-bid™ 12

(theophylline, anhydrous)

Nothing beats our system

From the makers of Azmacort™ (triamcinolone acetonide)

Please see next page for brief summary of prescribing information.

©1989 Rorer Pharmaceutical Corporation
Printed in U.S.A. FC#89-40 SB06189A 1/89

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA. U.S.A. 19034

Slo-bid

(theophylline, anhydrous)
50 mg, 100 mg, 200 mg, and 300 mg

Gyrocaps®
Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 100 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 μg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 μg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 μg/mL.

Information for Patients:
The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:
Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Rifampin	Decreased serum theophylline levels

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromotography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C – Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

Safety and effectiveness of Slo-bid Gyrocaps administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea.

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

50 mg – Clear (cap) and opaque white (body) capsule with 50 printed in red
100 mg – Clear capsule with 100 printed in red
200 mg – Opaque white (cap) and clear (body) capsule with 200 printed in red
300 mg – Opaque white capsule with 300 printed in red

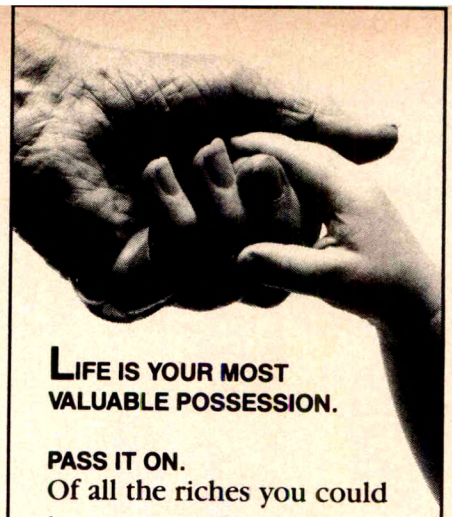
Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0057-99) and in unit dose 10 x 10 (NDC 0075-0057-62). Slo-bid Gyrocaps 100 mg are available in bottles of 100 (NDC 0075-0100-00), bottles of 1000 (NDC 0075-0100-99) and in unit dose 10 x 10 (NDC 0075-0100-62). Slo-bid Gyrocaps 200 mg are available in bottles of 100 (NDC 0075-0200-00), bottles of 1000 (NDC 0075-0200-99) and in unit dose 10 x 10 (NDC 0075-0200-62), and Slo-bid Gyrocaps 300 mg are available in bottles of 100 (NDC 0075-0300-00), bottles of 1000 (NDC 0075-0300-99) and in unit dose 10 x 10 (NDC 0075-0300-62), and are manufactured by:

RORER PHARMACEUTICALS
a division of
Rorer Pharmaceutical Corporation
Fort Washington, PA, U.S.A. 19034

R O RORER E R

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

500



LIFE IS YOUR MOST VALUABLE POSSESSION.

PASS IT ON.
Of all the riches you could leave to your family, the most precious is the gift of life. Your bequest to the American Heart Association assures that priceless legacy by supporting research into heart disease prevention.

To learn more about the Planned Giving Program, call us today. It's the first step in making a memory that lasts beyond a lifetime.

WE'RE FIGHTING FOR YOUR LIFE

American Heart Association

This space provided as a public service.

Picture of the Month

Brian J. Wiatrak, MD, Charles M. Myer III, MD (*Contributors*); Murray Feingold, MD (*Section Editor*)

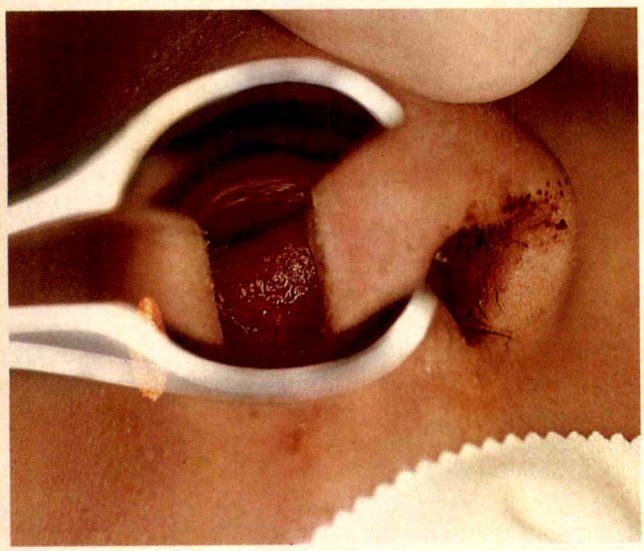


Figure 1.

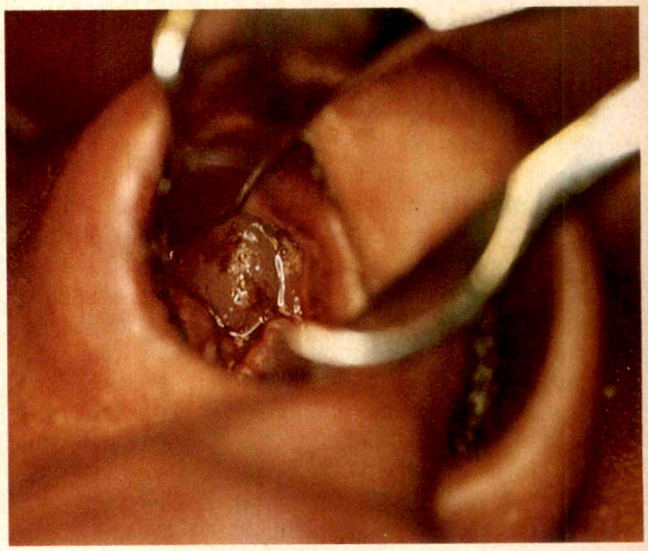


Figure 2.

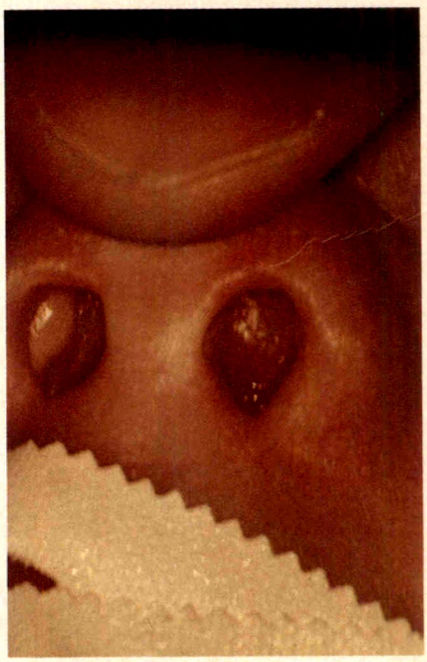


Figure 3.

The statements listed below are best associated with which of the above figures:

(*a*) Following nasal trauma, this lesion is associated with progressive nasal obstruction.

(*b*) This mass is a cause of nasal obstruction in patients with allergic rhinitis or chronic sinusitis.

(*c*) This condition should be considered in the differential diagnosis of any newborn or infant with nasal obstruction.

Accepted for publication December 1, 1988.

Contributed from the Department of Otolaryngology and Maxillofacial Surgery, University of Cincinnati (Ohio).

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—Nasal septal abscess.

Fig 2.—Inflammatory nasal polyps.

Fig 3.—Intranasal glioma.

A nasal septal abscess should be considered in patients presenting with progressive nasal obstruction following nasal trauma. The abscess usually presents as an erythematous, tender nasal mass that may completely obstruct the airway either unilaterally or bilaterally (Fig 1). The treatment of choice is incision and drainage with the placement of a drain and nasal packing. Septal hematomas may progress to suppuration and ultimately dissolution of the septal cartilage. This may occur as early as 48 hours, resulting in a long-term cosmetic deformity.

Inflammatory polyps of the nose usually present with progressive nasal obstruction, rhinorrhea, and other symptoms characteristic of chronic sinusitis. On physical examination, the polyps appear as gray, translucent masses usually located above the inferior turbinate (Fig 2). They most commonly arise from the ethmoid sinus. There may be an associated history of allergic rhinitis, asthma, aspirin intolerance, or chronic purulent rhinorrhea. Nasal polyps are noted in approximately 10% of patients with cystic fibrosis. Treatment consists of intranasal steroid preparations, allergy desensitization, and surgical extirpation.

Nasal gliomas and encephaloceles are protrusions of cranial contents through a bony defect in the skull; encephaloceles maintain their meningeal connection to the intracranial ventricular system, whereas gliomas do not. Nasal gliomas are associated with a fibrous stalk extending intracranially approximately 20% of the time. About 30% of gliomas present as intranasal masses (Fig 3). The mass is usually excised via a combined frontal craniotomy-intranasal approach. Although these lesions usually present soon after birth with symptoms of nasal obstruction, they may elude detection until later in infancy.

References

1. Myer CM III, Cotton RT. Nasal obstruction in the pediatric patient. *Pediatrics.* 1983;72:766-777.
2. Kramer RI. Otolaryngologic complications of cystic fibrosis. *Otolaryngol Clin North Am.* 1977;10:205-208.
3. Hughes GB, Shapiro G, Hunt W. Management of the congenital midline nasal mass: a review. *Head Neck Surg.* 1980;2:222-233.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Avenue, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Radiological Case of the Month

William A. Bonadio, MD (*Contributor*); Beverly P. Wood, MD (*Section Editor*)

Accepted for publication May 17, 1988.

Contributed from the Department of Pediatrics, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee.

Reprint requests to Box 648, Department of Radiology, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

A previously well 5-month-old male infant presented to the emergency department with a one-day history of cough and choking with feedings. There were several episodes of retching without emesis. On physical examination, the patient was in no distress and vital signs were normal. Auscultation of the lungs revealed the presence of bowel sounds. The abdomen was soft, not distended or tender, with normoactive bowel sounds. A roentgenogram of the chest was obtained (Fig 1). After review of the initial roentgenographic findings, a nasogastric tube was passed, and another roentgenogram of the chest was obtained (Fig 2).

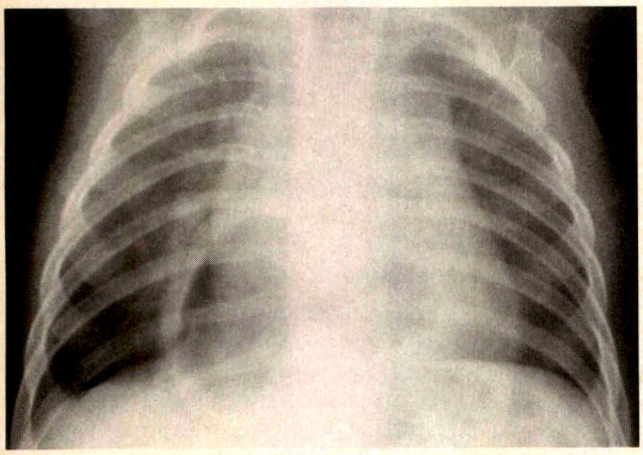


Figure 1.

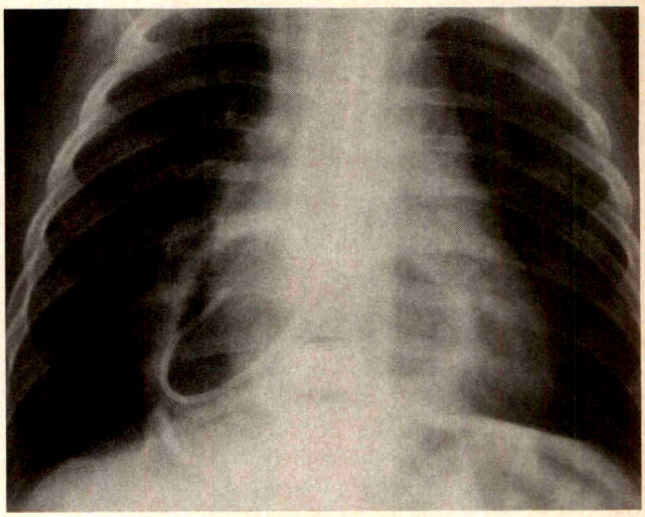


Figure 2.

Denouement and Discussion

Intrathoracic Stomach With Volvulus

Fig 1.—Anteroposterior chest roentgenogram shows large, dumbbell-shaped gas collection in mediastinum.

Fig 2.—Anteroposterior roentgenogram of chest after nasogastric tube placement confirms that gas is gastrointestinal, communicating via esophagus.

Fig 3.—Barium contrast study of upper gastrointestinal tract shows entire stomach within thorax, rotated, and pylorus entering diaphragmatic hiatus (arrow).

The initial chest roentgenograms (Figs 1 and 2) showed a large, intrathoracic, gas-filled viscus (stomach) located immediately above the diaphragm in the mediastinum. An upper-gastrointestinal-tract study confirmed the presence of an intrathoracic stomach and documented an associated 180° organoaxial volvulus of the stomach with herniation through the diaphragmatic hiatus. The pylorus is located at the diaphragmatic hiatus (Fig 3).

Acute gastric volvulus is a rare entity in children. While cases occur in adults in the fifth decade of life, approximately half of the cases recorded are congenital. Tanner[1] proposed a list of predisposing causes of gastric volvulus, including ligamentous laxity, bands and adhesions, and hernias through defects of the diaphragm. The clinical features of this disorder depend on the type of volvulus encountered. With mesenteroaxial volvulus, the stomach rotates anteriorly on a vertical axis, producing a characteristic "backwards" stomach. Borchardt[2] emphasized a triad of symptoms characterizing this disorder: (1) severe epigastric pain and distension, (2) vomiting followed by retching without emesis, and (3) inability to pass a nasogastric tube. In organoaxial volvulus, the stomach inverts along its long axis, with the greater curve becoming superior and the lesser curve inferior. Carter et al[3] described a triad of symptoms characterizing this disorder: (1) minimal abdominal findings, (2) a gas-filled viscus in t chest, and (3) partial obstr the gastric antrum delineat upper-gastrointestinal-tract With either type of gastric twisting and obstruction ma tial and/or intermittent. Whe teroaxial volvulus causes occ both the pylorus and cardia v promise of the blood suppl surgical emergency is at hanc ing immediate operative de sion to avoid acute gastric ne is recommended that fixatic stomach be accomplished by gastropexy; this will preven currence of volvulus.[1,5]

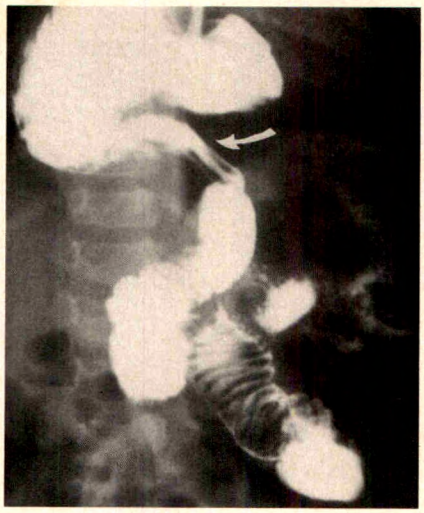


Figure 3.

References

1. Tanner NC: Chronic and recurre of the stomach with late results of placement.' *Am J Surg* 1968;115:505-
2. Borchardt M: Zum Pathologie ur des Magnevolvulus. *Arch Klin Chir* 1 254.
3. Carter R, Brewer LA, Hinshaw gastric volvulus: A study of 25 cases. 1980;140:99-106.
4. Gerson DE, Lewicki AM: In stomach: When does it obstruct? 1976;119:257-264.
5. Cole BC, Dickinson SJ: Acute the stomach in infants and childre 1971;70:707-717.

The Editors welcome contributions to PICTURE OF THE MONTH and RADIOLOGICAL CASE OF THE MONTH. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Avenue, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

When I was a child there was no Orimune®

Poliovirus Vaccine Live, Oral Trivalent

Jackie DiLorenzo of Hastings-on-Hudson, New York, contracted polio in 1950, before a vaccine became available. She spent ten years in rehabilitation, during which time she underwent nine operations on her spine, legs and feet. Jackie currently lives in a house adapted for wheelchair living.

Lederle Biologicals Protecting Families Through Immunization®

Please see following page for brief summary of prescribing information.

When I was a child there was no Orimune®

Proven in Millions of US Patients

ORIMUNE was the first live, oral, trivalent polio vaccine. No other oral polio vaccine has done more to help eradicate wild poliovirus in the US. Approximately 500 million doses have been distributed to date.

Proven Safety Record*

Lederle takes every precaution during production and testing to ensure the safety of ORIMUNE. This dedication is evident by our 25-year safety record.

Uninterrupted Supply

Lederle has consistently met the nation's needs for oral polio vaccine for about 25 years. In fact, when all other US manufacturers discontinued the production of oral polio vaccine, Lederle has remained committed to this essential product and to the health of America's children.

Available in Single-Doses

ORIMUNE is available in convenient, unit-dose DISPETTES® to help assure dosage accuracy and avoid the risk of contamination.

*See adverse reactions section of brief summary

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

A Brief Summary

Please see package insert for full description, directions for use, and references.

INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*
CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev. 8/86

Orimune®
Poliovirus Vaccine Live, Oral Trivalent

Lederle Biologicals®
Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470
© 1988 Lederle Laboratories
603-8

Video*Demonstration*
Video*Instruction*
Video*Enactment*

The AMA Video Clinic library of videotapes can expand your understanding with the latest on the diagnosis and treatment of more than 40 medical conditions.

AMA Video Clinic programs are produced in exciting, informative formats. Leading national experts will guide you through actual and simulated clinical procedures, role plays, demonstrations, interviews and more.

Find out more. Call 1-800-621-8335. In Illinois call collect 312-645-4987.

AMA*VideoClinic*

Expand your art by expanding your science.

The Pediatrics Board Review Course

April 6-12, 1989 — Nashville
May 26-31, 1989 — Louisville
September 26-October 1, 1989 — Chicago
Now, your only BOARD REVIEW just before Written and Oral Exams

OBJECTIVES:
- Improve basic and clinical knowledge in pediatrics
- Assist residents and fellows in organizing study
- Prepare candidates to take examinations
- Provide practicing pediatricians with a review and update

METHODS:
- HOME STUDY MATERIALS with a syllabus of questions and answers — and assignments
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

NEONATOLOGY
Growth and Development
Nutrition
Fetal Diagnosis
Newborn Diseases
Critical Care

IMMUNOLOGY
Immune Physiology
Immunodeficiency
Allergy
Rheumatology

INFECTIOUS DISEASES
Immunizations
Bacterial Infections
Viral Infections
Mycotic Infections
Parasitic Infections

CARDIOLOGY
Cardiac Evaluation
Congenital Diseases
Acquired Diseases
Arrhythmias

GASTROENTEROLOGY
Upper GI Tract
Malabsorption
Small and Large Bowel
Liver and Gall Bladder
Pancreas

NEPHROLOGY
Glomerular Nephridities
Nephrotic Syndrome
Urinary Tract Infections
Renal Hypertension
Congenital Uropathies

ENDOCRINOLOGY
Hypothalamus/Pituitary
Thyroid and Parathyroid
Adrenal Disorders
Gonadal Disorders
Diabetes/Hypoglycemia

HEMATOLOGY-ONC.
Red Cell Disorders
White Cell Disorders
Platelets and Coagulation
Solid Tumors

NEUROLOGY
Convulsive Disorders
Congenital Diseases
Acquired Diseases
Neuromuscular Diseases

PSYCHOLOGY
Psychological Development
Psychiatric Disorders
Child Abuse
Substance Abuse

GENETICS AND OTHER
Chromosomal Anomalies
Errors of Metabolism
Morphologic Syndromes
Poisoning
Pulmonology

OTHER SPECIALTIES
Orthopedics
Dermatology
Ophthalmology
Otolaryngology
Radiology

L. Garret Adams, M.D.
Associate Professor of Pediatrics
University of Louisville †‡

Henrietta Bada, M.D.
Professor of Pediatrics & Ob-Gyn.
University of Tennessee †

Anin Barakat, M.D.
Associate Professor of Pediatrics
Vanderbilt University †

Robert Baumann, M.D.
Associate Professor of Neurology
University of Kentucky †‡

Peter Dignan, M.D.
Professor of Pediatrics
Vanderbilt University ‡

Craig Douglas, M.D.
Ass't. Clin. Professor of Pediatrics
University of Louisville ‡

Robert Estes, M.D.
Visiting Prof. of Ophthalmology
University of Tennessee †

Michael Foster, M.D.
Assistant Professor of Pediatrics
University of Louisville ‡

Harold Harrison, M.D.
Associate Professor of Pediatrics
University of Louisville ‡

Robert Hunt, M.D.
Associate Professor of Psychiatry
Vanderbilt University ‡

William Meyer, M.D.
Associate Professor of Pediatrics
University of Tennessee †‡

Gordon Moreau, M.D.
Assistant Professor of Pediatrics
Vanderbilt University †

Jennifer Najjar, M.D.
Assistant Professor of Pediatrics
Vanderbilt University †

Paul Parker, M.D.
Professor of Pediatrics
University of Mississippi †‡

John Phillips, M.D.
Prof. of Pediatrics & Biochemistry
Vanderbilt University †

Allan Rees, M.D.
Associate Professor of Pediatrics
University of Louisville ‡

Shirley Wilkerson, M.D.
Ass't. Prof. of Pediatrics &Ob-Gyn.
University of Louisville ‡

Judy Willemas, M.D.
Associate Professor of Pediatrics
University of Tennessee †‡

Larry Williams, M.D.
Assistant Professor of Pediatrics
University of Arkansas †‡

† faculty for the Nashville course
‡ faculty for the Louisville course

*"Accommodations were comfortable..."**

GOALS AND LOCATION: The course is held the week before oral and written board exams. Sites are chosen for excellent study and minimal cost of hotel and travel for board candidates. Home study questions will be sent before the course and answers are sent after completing your assignment. Your best value is to repeat the seminar for half price the week before your written or oral exam. The Nashville meeting will be at the Holiday Inn — Airport, Nashville, TN. Our room rates are $79 single and $89 double.

*"...and those little extras...."**

LOWEST AIR FARES: Reliable Travel offers you the lowest air fare — often below super-saver rates. Please call toll-free 1-800-645-6504 ext. 10 and identify yourself with this Osler course for special group fares.

*"...remarkably complete and pleasant."**

PLACEMENT SERVICE: For a practice opportunity write or call (800) 356-7537.

*"...the most education for the money."**

FEES AND C.M.E. CREDITS:
- **C.M.E. Credit: 60 hrs.**
- Practicing Pediatrician: $660
- Residents and Fellows: one third off
- Repeating course within 3 years: half price
- **Add 10% within 10 days of course.**
- Attendees not in course hotel add $8/day.
- $50.00 will reserve your position.

*"...home study material was extremely helpful."**

CANCELLATIONS: Refunds subject to $50 fee, will be made until the seminar begins.
- Cancellation after mailing home study material requires retention of half of the fee.

*"I feel [the course] helped me pass the boards."**

INFORMATION:

Joseph H. Selliken Jr., M.D.
THE OSLER INSTITUTE
1094 Dawn Lane, Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

Limited Enrollment: PEDIATRICS BOARD REVIEW REGISTRATION

Name _____

Address _____

City/State/Zip _____

Phone _____

For: ☐ April 6-12, 1989 — Nashville
☐ May 26-31, 1989 — Louisville
☐ Sept. 26-Oct. 1, 1989 — Chicago

☐ Check is enclosed for $ _____

☐ Please send more information.

Mail today to:
1094 Dawn Lane, Dept A4
P.O. Box 2218
Terre Haute, IN 47802

**Comments by participants of our courses*

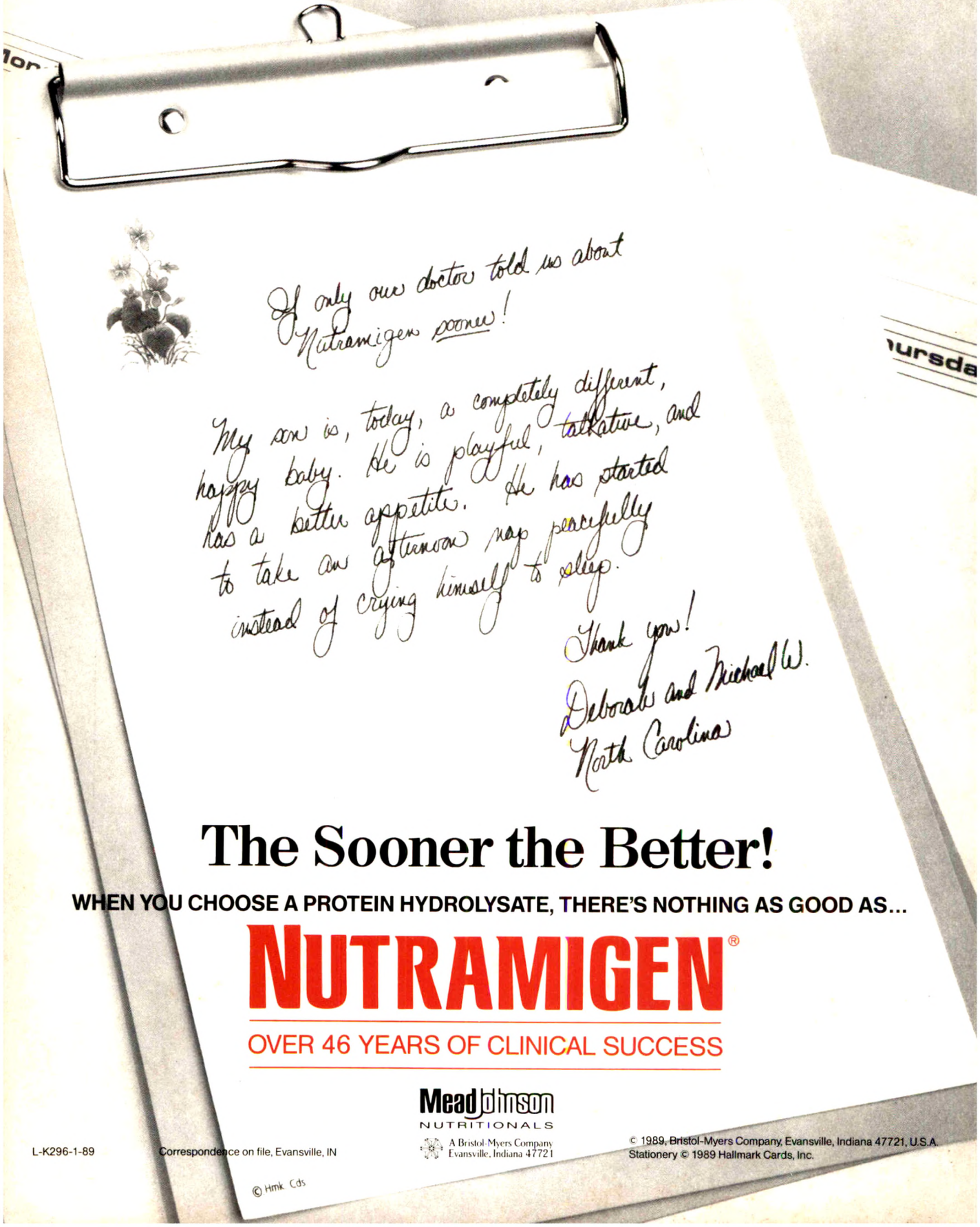
Published by the American Medical Association

May 1989
Volume 143, Number 5

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

THE PEDIATRIC FORUM		517
LEADS FROM THE MMWR		525
EDITORIALS: Is Standard Practice in Pediatrics 'Standard'?	*V. A. Fulginiti*	529
Dietary Advice	*L. Finberg*	531
Current State of Pertussis Vaccines	*V. A. Fulginiti*	532
THE EDITORIAL BOARD SPEAKS . . . : Thank You Robin and Richard	*A. W. Pruitt*	534
ARTICLES: Growth Failure From Dietary Advice	*F. Lifshitz et al*	537
Tracheobronchial Foreign Bodies	*H. Puhakka et al*	543
Pediatric Coin Ingestions	*J. E. Schunk et al*	546
Pediatric Coin Ingestion	*E. M. Caravati et al*	549
Physiotherapy for Children With Cerebral Palsy	*E. Tirosh et al*	552
Risk Factors in Unintentional Injuries	*C. C. Bourguet et al*	556
SPORTS MEDICINE: Strength, Flexibility, and Maturity in Adolescent Athletes	*M. Pratt*	560
ARTICLES: Smoking Policy in Pediatric Hospitals and Wards	*J. A. Jenista*	567
Ebstein's Anomaly and Extracardiac Defects	*J. R. Siebert et al*	570
EDUCATIONAL INTERVENTIONS: Students' Clinical Reasoning Using a Computer	*W. Schwartz*	575
ARTICLES: *Staphylococcus epidermidis* in Blood and Spinal Fluid	*J. Gruskay et al*	580
Prenatal Cocaine Exposure	*I. J. Chasnoff et al*	583
Behavior Patterns During Breast- and Bottle-feeding	*O. P. Mathew et al*	588
REVIEW: Secondary Disorders of the Complement System	*L. F. Eichenfield et al*	595
ARTICLES: Transient Erythroblastopenia of Childhood	*T. Hays et al*	605
Abnormal Zinc Content in Human Milk	*S. A. Atkinson et al*	608
DRGs Children, and Race	*E. Munoz et al*	612
Organ Injury After Asphyxia	*J. M. Perlman et al*	617
SPECIAL FEATURES: Picture of the Month	*P. R. Cohen et al*	621
Radiological Cases of the Month	*E. Barzel et al*	623
	S. H. Fang et al	625

A Note from "Mom":



The Sooner the Better!

WHEN YOU CHOOSE A PROTEIN HYDROLYSATE, THERE'S NOTHING AS GOOD AS...

NUTRAMIGEN®

OVER 46 YEARS OF CLINICAL SUCCESS

Mead Johnson NUTRITIONALS

A Bristol-Myers Company
Evansville, Indiana 47721

L-K296-1-89

Correspondence on file, Evansville, IN

© 1989, Bristol-Myers Company, Evansville, Indiana 47721, U.S.A.
Stationery © 1989 Hallmark Cards, Inc.

Ryan's running, thanks to a miracle!

Ten-year-old Ryan Shewell contracted pneumococcus septicemia at age 9. Upon admission to Children's Hospital and Medical Center in Seattle, physicians discovered that Ryan was born without a spleen. Debridement surgeries saved Ryan's life... but both legs were amputated below the knee. Today, with prostheses and physical therapy, Ryan is back to playing soccer with his friends. His family gives thanks to Ryan's unfailing spirit... and to the hospital, funded in part by Children's Miracle Network.

The Children's Miracle Network Telethon is the one national fund-raising appeal specifically for hospitals for children throughout the United States and Canada. In 1988, the telethon raised over $60 million, making it the largest telethon.

One hundred percent of the money raised goes directly to individual hospitals for children...so that miracles like Ryan's can happen for the 5,000,000 children treated each year.

Children's Miracle Network

Sponsored in part by

CHILDREN'S TYLENOL®
acetaminophen

Share In The Caring

© McN. 1989

McNeil Consumer Products Company
Division of McNeil-PPC, Inc.
Fort Washington, PA 19034

McNEIL

For clean, protected skin

Baby Magic® Baby Bath

- Clinically proven hypo-allergenic[1]
- pH balanced to match babies' skin[1]
- Cleans gently without removing natural skin oils
- Milder than the leading bar soap[1]
- Tear-free

Baby Magic® Baby Lotion

- Clinically proven hypo-allergenic[1]
- pH balanced to match babies' skin[1]
- Special moisturizers leave babies' skin soft
- Helps protect against irritating wetness in the diaper area

1. Data on file, The Mennen Company.

Call 1-800-325-7654 to receive a Baby Magic® clinical overview.

T E S T E D B Y S C I E N C E A N D T I M E

by MENNEN

©1989 The Mennen Co.

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOL 143 NO. 5 May 1989

Copyright © 1989 by the American Medical Association

Monthly Circulation >44 500
Also published in French

THE PEDIATRIC FORUM

517 **Pediatricians' Recommendations for Antipyretic Agents With DTP Immunizations: A Survey of Current Practice** Patricia J. Flanagan, MD; Anthony J. Alario, MD; John S. O'Shea, MD; Georges Peter, MD, Providence, RI . . . **Adolescents' Knowledge and Beliefs About AIDS: Did the Government Brochure Help?** Gregory D. Zimet, PhD; Trina M. Anglin, MD, PhD; Rina Lazebnik, MD; Debra Bunch, MD; Paul Williams, MD; Daniel P. Krowchuk, MD, Cleveland, Ohio . . . **Interactions of Alcohol and Nutrition** Roque M. C. da Cunha Ferreira, MD, Lisboa, Portugal . . . **Tack Up a Warning on TAC** Howard C. Mofenson, MD; Thomas R. Caraccio, PharmD, East Meadow, NY . . . **Telephone Etiquette: The Telephone, One of the Physician's Most Necessary and, at Times, Most Hated Devices** Gunnar B. Stickler, MD, Rochester, Minn . . . **Prolonged Intravenous Infusions** Jeffrey B. Sussmane, MD, Miami, Fla, Robert J. Shulman, MD, Houston, Tex . . . **Research During Residency** Robert J. Winter, MD, Chicago, Ill . . . **Prolactinoma in an Adolescent Girl: Unusual Response to Bromocriptine Therapy** . . . Chandra M. Tiwary, MBBS, MA, MBA, San Antonio, Tex

525 **LEADS FROM THE MMWR**

EDITORIALS

529 **Is Standard Practice in Pediatrics 'Standard'?**
Vincent A. Fulginiti, MD, New Orleans, La

531 **Dietary Advice**
Laurence Finberg, MD, Brooklyn, NY

532 **The Current State of Pertussis and Pertussis Vaccines**
Vincent A. Fulginiti, MD, New Orleans, La

THE EDITORIAL BOARD SPEAKS . . .

534 **Thank You Robin and Richard**
Albert W. Pruitt, MD, Washington, DC

ARTICLES

537 **Growth Failure**
Fima Lifshitz, MD, Nancy Moses, MNS, RD, Manhasset, NY

543 **Tracheobronchial Foreign Bodies**
Heikki Puhakka, MD; Erkki Svedström, MD; Pentti Kero, MD; Päivi Valli, BM; Eila Iisalo, MD, Turku, Finland

546 **Pediatric Coin Ingestions**
Jeff E. Schunk, MD, Los Angeles, Calif;
Howard Corneli, MD, Robert Bolte, MD, Salt Lake City, Utah

549 **Pediatric Coin Ingestion**
E. Martin Caravati, MD; Don L. Bennett, RPh;
Newell E. McElwee, PharmD, Salt Lake City, Utah

552 **Physiotherapy for Children With Cerebral Palsy**
Emanuel Tirosh, MD, Sheri Rabino, MSc, Haifa, Israel

556 **Unintentional Injuries**
Claire C. Bourguet, PhD, Robert E. McArtor, MD, MPH, Rootstown, Ohio

Continued on p 512.

EDITORIAL BOARD

Editor
Vincent A. Fulginiti, MD
American Journal of
Diseases of Children
Dean's Office
Room 1529
Tulane University
School of Medicine
1430 Tulane Avenue
New Orleans, LA 70112
(504) 584-1989

Associate Editors
Thomas G. Storch, MD
New Orleans, La
William W. Waring, MD
New Orleans, La

Book Review Editor
Peggy C. Ferry, MD
Tucson, Ariz

Administrative Assistant
Joann M. Quane
New Orleans, La

Secretary
Laura Martin
Tucson, Ariz

Hugh D. Allen, MD, Columbus, Ohio
Milton I. Arnold, MD, Los Angeles, Calif
Alan D. Bedrick, MD, Tucson, Ariz
Richard W. Blumberg, MD, Atlanta, Ga
Ben H. Brouhard, MD, Cleveland, Ohio
George W. Brown, MD, Los Lunas, NM
James J. Corrigan, Jr, MD, Tucson, Ariz
Beverly B. Dahms, MD, Cleveland, Ohio
Murray Feingold, MD, Boston, Mass
Patricia Ferrieri, MD, Minneapolis, Minn
Laurence Finberg, MD, Brooklyn, NY
Boyd W. Goetzman, MD, PhD, Davis, Calif
John D. Johnson, MD, Albuquerque, NM
James P. Keating, MD, St Louis, Mo
Elizabeth R. McAnarney, MD, Rochester, NY
Dan G. McNamara, MD, Houston, Tex
Beverly C. Morgan, MD, Orange, Calif
Henry L. Nadler, MD, Chicago, Ill
Robert Penny, MD, Los Angeles, Calif
Albert W. Pruitt, MD, Augusta, Ga
Kenneth B. Roberts, MD, Worcester, Mass
Barton D. Schmitt, MD, Denver, Colo
E. Richard Stiehm, MD, Los Angeles, Calif
William B. Strong, MD, Augusta, Ga
Beverly P. Wood, MD, Rochester, NY

Continued from p 511.

SPORTS MEDICINE

560 **Strength, Flexibility, and Maturity in Adolescent Athletes**
Michael Pratt, MD, MS, Seattle, Wash

ARTICLES

567 **Smoking Policy in Pediatric Hospitals and Wards**
Jerri Ann Jenista, MD, Ann Arbor, Mich

570 **Ebstein's Anomaly and Extracardiac Defects**
Joseph R. Siebert, PhD, Seattle, Wash; Mason Barr, Jr, MD, Ann Arbor, Mich; J. Craig Jackson, MD; Denis R. Benjamin, MB, BCh, Seattle, Wash

EDUCATIONAL INTERVENTIONS

575 **Documentation of Students' Clinical Reasoning Using a Computer Simulation**
William Schwartz, MD, Philadelphia, Pa

ARTICLES

580 **Neonatal *Staphylococcus epidermidis* Meningitis With Unremarkable CSF Examination Results**
Jeffrey Gruskay, MD; Mary Catherine Harris, MD; Andrew T. Costarino, MD; Richard A. Polin, MD; Stephen Baumgart, MD, Philadelphia, Pa

583 **Prenatal Cocaine Exposure Is Associated With Respiratory Pattern Abnormalities**
Ira J. Chasnoff, MD; Carl E. Hunt, MD; Ron Kletter, PhD; David Kaplan, MD, Chicago, Ill

588 **Sucking and Breathing Patterns During Breast- and Bottle-feeding in Term Neonates**
Oommen P. Mathew, MD, Jatinder Bhatia, MD, Galveston, Tex

REVIEW

595 **Secondary Disorders of the Complement System**
Lawrence F. Eichenfield, MD, Richard B. Johnston, Jr, MD, Philadelphia, Pa

ARTICLES

605 **Transient Erythroblastopenia of Childhood**
Taru Hays, MD, Peter A. Lane, Jr, MD, Denver, Colo; Frank Shafer, MD, Washington, DC

608 **Abnormal Zinc Content in Human Milk**
Stephanie A. Atkinson, PhD; Donald Whelan, MD, FRCPC; Robin K. Whyte, MB, FRCPC, Hamilton, Canada; Bo Lönnerdal, PhD, Davis, Calif

612 **Pediatric Patients, Race, and DRG Prospective Hospital Payment**
Eric Munoz, MD, MBA; Eugenio Barrios, MS; Houston Johnson, MD; Jonathan Goldstein, MPA; Katherine Mulloy, AS; Donald Chalfin, MD; Leslie Wise, MD, New Hyde Park, NY

617 **Acute Systemic Organ Injury in Term Infants After Asphyxia**
J. M. Perlman, MD; E. D. Tack, MD; T. Martin, MD; G. Shackelford, MD; E. Amon, MD, St Louis, Mo

Continued on p 514.

The AMERICAN JOURNAL OF DISEASES OF CHILDREN is a member of the consortium of AMA journals listed below. The Archives reaches more than 41 500 readers in 85 countries each month. The complete text of all AMA journals is available on the MEDIS data base from Mead Data Central, Dayton, Ohio.

JAMA The Journal of the American Medical Association

AJDC American Journal of Diseases of Children

archives of **Dermatology**

archives of **General Psychiatry**

archives of **Internal Medicine**

archives of **Neurology**

archives of **Ophthalmology**

archives of **Otolaryngology-Head & Neck Surgery**

archives of **Pathology & Laboratory Medicine**

archives of **Surgery**

James H. Sammons, MD, Executive Vice-President

James S. Todd, MD, Senior Deputy Executive Vice-President

Kenneth E. Monroe, Deputy Executive Vice-President

Theodore R. Chilcoat, Jr, Assistant Executive Vice-President

M. Roy Schwarz, MD, Assistant Executive Vice-President

George D. Lundberg, MD, Vice-President, Scientific Information

John T. Baker, Vice-President, Publishing

Norman D. Richey, Director, Publication Production and Printing Division

Lee A. Parent, Director, Circulation-Fulfillment Division

Dennis Joseph Dennehy, Director, Advertising Sales and Promotion Services Division

Thomas J. Carroll, Director, Department of Advertising Communication

Raymond Christian, Director, Advertising Services Department

ALIMENTUM™

Protein Hydrolysate Formula With Iron

For the dietary management of infants with protein sensitivity, carbohydrate malabsorption, and fat malabsorption.

The only ready-to-feed casein hydrolysate infant formula that combines convenience with formulation advantages to meet all your hydrolysate feeding needs.

- A caloric distribution similar to that of breast milk.
- An extensively hydrolyzed infant formula with proven hypoallergenicity.
- A dual source of carbohydrate at an appropriate level to minimize the risk of carbohydrate intolerance.
- Fifty percent of the fat from medium-chain triglycerides — an easily digested and absorbed fat source.

Meeting All Your Hydrolysate Feeding Needs

© 1988 Ross Laboratories

ROSS LABORATORIES
COLUMBUS, OHIO 43216
Division of Abbott Laboratories, USA

B101/8890

PUBLICATION STAFF
Offices: 535 N Dearborn St
Chicago, IL 60610

Managing Editor and Director, AMA Specialty Journals:
Michael D. Springer

Associate Editor:
Julie Foreman

Production Manager:
Marlene M. Hinsch

Assistant Production Manager:
John R. Sayban

Editorial Processing Manager:
Cheryl Iverson

Assistant Editorial Processing Manager:
Paula Glitman

Permissions and Graphic Design Manager:
Dennis J. Shipley

Staff Assistants:
Diane Darnell
Bonnie Van Cleven

Copy editing:
Patricia A. Predey (Supervisor)
Vickey Golden (Free-lance Coordinator)
Paul Frank (Senior Copy Editor)
John Radanovich

Production Supervisors:
Betty Frigerio (Advertising)
Thomas J. Handrigan (Illustrations)
Elizabeth Petrikenas (Proofreading)
Mary C. Steermann (Editorial)
JoAnne Weiskopf (Layout)

Proofreading:
Teresa H. Omiotek
Richard T. Porter
Jennifer Reiling
Barbara Wojtowicz

Art and Senior Production Assistants:
Melinda Arcabos
Cari Biamonte
Laura Bleiler
Karen Branham
Cynthia Gelper
Jerri Hall-Gortowski
Anita Henderson
Debra Lucas
Juliana K. Mills
Dorothy Patterson
Susan Price
E. Ruth White
Ellen Yoshihara

Production Assistant:
Darlene E. Filips

Editorial Assistant:
Jean Schaffner

Department of Scientific and Socioeconomic Indexing:
Norman Frankel (Director)
George Kruto
Susan McClelland
Mary Kay Tinerella

Please address communications concerning accepted or published communications to AMA Specialty Journals, 535 N Dearborn St, Chicago, IL 60610.

EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

Continued from p 512.

SPECIAL FEATURES

621 **Picture of the Month**
Philip R. Cohen, MD, Michael Yunakov, MD (*Contributors*), New York, NY; Murray Feingold, MD (*Section Editor*), Brighton, Mass

623 **Radiological Cases of the Month**
Eval Barzel, MD, Jack O. Haller, MD (*Contributors*), Brooklyn, NY; Beverly P. Wood, MD (*Section Editor*), Rochester, NY

625 Swee H. Fang, MBBS, MRCP(UK); R. Ocejo, MD, FRCPC; Margaret Sin, MBBS, FRCPC; Neil N. Finer, MD, FRCPC (*Contributors*), Edmonton, Canada; Beverly P. Wood, MD (*Section Editor*), Rochester, NY

BOOK REVIEWS

Textbook of Critical Care (Shoemaker, Ayres, Grenvik, et al, eds) Reviewed by Robert A. Berg, MD, Tucson, Ariz (p 551) . . . **Books Received but Not Reviewed**

516 **INSTRUCTIONS FOR AUTHORS**

574 **INDEX TO ADVERTISERS**

CORRECTIONS

587 **Advances in Pediatric Cardiology**
Beverly C. Morgan, MD, Orange, Calif

592 **The Pediatric Forum: Cutis Verticis Gyrata and Chromosomal Abnormalities**
Marini Romana, MD, Marco Cappa, MD, Rome, Italy; Giovanni Neri, MD, Chieti, Italy

AJDC, American Journal of Diseases of Children (ISSN 0002-922X) is published monthly by the American Medical Association, 535 N Dearborn St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

SUBSCRIPTION RATES—The subscription rates for the American Journal of Diseases of Children are as follows: $48 for one year, $81 for two years in the United States and US Possessions; all other countries, one year, $58; two years, $101 for surface delivery. (For expedited air delivery to most countries, add $15 surcharge for one year subscription, $30 for two years.) Rates for subscriptions for delivery to Japan or South Korea are available through exclusive agents—contact the publisher. ***Special rates for residents and medical students in the United States and US Possessions are available.*** Address inquiries to the American Medical Association, Circulation and Fulfillment Division, 535 N Dearborn St, Chicago, IL 60610. Phone: (312) 280-7168.

CHANGE OF ADDRESS—POSTMASTER, send all address changes for AJDC, American Journal of Diseases of Children. Attention: Subscription Department, 535 N Dearborn St, Chicago, IL 60610. Notification of address change must be made at least six weeks in advance, include both old and new addresses, a recent mailing label, and your new zip code.

ADVERTISING OFFICES: Eastern: 600 Third Ave, Suite 3700, New York, NY 10016 (**Manager:** Robert C. Corcoran [212-867-6640]; **Representative:** Phillip B. Altamore); **Midwest/Farwest:** 535 N Dearborn St, Chicago, IL 60610 (**Manager:** Thomas J. Carroll [312-280-7182]; **Representative:** John P. Cahill, Midwest/Farwest)

Advertising Principles: Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.

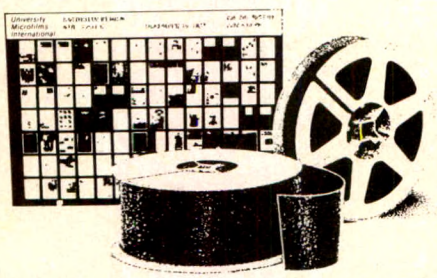
CONGENITAL ADRENAL HYPERPLASIA REFERRAL

The Clinical Center requests the cooperation of physicians in the referral of growing children with congenital adrenal hyperplasia for a study on the relative effectiveness of once-daily compared to twice-daily hydrocortisone administration. The bone age must be ≤ 11 years for boys and ≤ 9 years for girls.

Patients will be followed in conjunction with their referring physicians over the 2-year duration of the study. At the completion of the study patients will be returned to the care of their referring physician. Please write or telephone:

Dr. Louisa Laue or
Dr. Gordon B. Cutler, Jr.
Building 10, Room 10N-262
National Institutes of Health
Bethesda, Maryland 20892
Tel: (301) 496-4686

this publication is available in microform



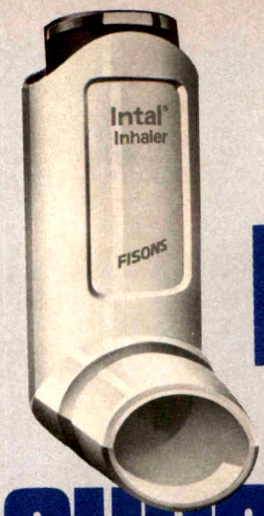
Please send me additional information.

University Microfilms International

300 North Zeeb Road
Dept. P.R.
Ann Arbor, MI 48106
U.S.A.

18 Bedford Row
Dept. P.R.
London, WC1R 4EJ
England

Name _____
Institution _____
Street _____
City _____
State _____ Zip _____



FORM AND SUBSTANCE ARE EVERYTHING

INTAL®

(cromolyn sodium/FISON

Available as

INTAL Inhaler **INTAL Capsules** with Spinhaler® Turbo-Inhaler **INTAL Nebulizer Sol**

FISONS
FISONS CORPORATION
BEDFORD, MA 01730

FIS-031

NEW MANUSCRIPT PROCEDURE

On Jan 1, 1988, *AJDC* initiated a new procedure. Manuscripts submitted to *AJDC* will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information.—Please send manuscripts and correspondence by first-class mail (*do not use registered, certified, or express mail*) to the Editor, Vincent A. Fulginiti, MD, *AJDC*, Dean's Office, Room 1529, Tulane University, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval *if requested* by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

Step 1.—*Cover Letter.*—All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNATURES):

1. *Copyright Release.*—"In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA."

2. *Statement of Affirmation.*—"This manuscript has not been published anywhere in any language and is not under simultaneous consideration by another publication. This manuscript is original and ALL authors have seen and approve of its contents."

3. *Financial Disclosure.*—List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg, employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of *AJDC*.

Step 2.—*Manuscript Format.*—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. *Do not use justified right margins.*

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with *each line, including headings, double-spaced.* Continuations should be on a second sheet with all headings repeated.

9. Use Système International (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed *label* and affixed on the back of each illustration. *Do not write directly on the print.*

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transparencies mounted transparencies or color prints. Fee is $400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from *both* parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, Williams E. Persistent fetal circulation: neurodevelopment outcome. *AJDC*. 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P. Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty. In: Conly J, Dickinson JT, eds. *Plastic and Reconstructive Surgery of the Face and Neck*. New York, NY: Grune & Stratton; 1972:84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

Authors are responsible for the accuracy of the references.

12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.

13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from *publisher* and *author.* Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3.—*Special Departments.*—Criteria for several special departments are given below.

1. *The Pediatric Forum.*—This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. *From Research to Relevance.*—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. *Educational Interventions.*—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

4. *Sports Medicine.*—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
- ____ 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors.
- ____ 3. Original typed manuscript plus three copies.
- ____ 4. Triple-spacing; double-spacing for tables and legends.
- ____ 5. Right margins UNJUSTIFIED.
- ____ 6. Title 75 characters or less.
- ____ 7. Abstract included.
- ____ 8. References in proper format, cited in numerical order.
- ____ 9. Four sets of illustrations.
- ____ 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- ____ 12. Permission forms for illustrations previously published elsewhere.

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

Pediatricians' Recommendations for Antipyretic Agents With DTP Immunizations: A Survey of Current Practice

Sir.—Febrile and local reactions to diphtheria and tetanus toxoids and pertussis (DTP) vaccine are a frequent and major concern to parents and a source of discomfort to children. Among the most common reactions is fever, which occurs in 47% of immunized children.[1] As a result, some pediatricians may empirically prescribe prophylactic antipyretic therapy at the time of vaccination. The extent of this practice has not been documented to our knowledge and, until recently, the benefit of such therapy has not been examined.

To assess the frequency of this practice, we conducted a survey of community-based pediatricians to determine whether, and under what circumstances, they recommended prophylactic antipyretic therapy for children receiving DTP vaccine. The survey was performed before recently published reports documented the effectiveness of prophylactic acetaminophen therapy with DTP immunization.[2,3] Despite the lack of studies documenting the usefulness of antipyretics, we anticipated that our survey would demonstrate that antipyretic agents were commonly recommended because of the perceived benign nature of the intervention, the respondents' familiarity with the drug, and an expectation on the part of practitioners that antipyretic prophylaxis would be effective.

Methods.—The survey, completed in April 1987, consisted of a one-page, mail-in anonymous questionnaire. The question that interested us (ie, recommendation of prophylactic antipyretics) was buried among five other items concerning fever management and anticipatory fever education. A single copy of the questionnaire was mailed to the 112 community-based pediatricians who were current members of the state chapter of the American Academy of Pediatrics or on the pediatric staff of Rhode Island's single major university-affiliated pediatric teaching hospital.

Results.—Seventy-three percent (82/112) of the pediatricians responded. Ninety-one percent (75/82) of the respondents said that they discussed fever and antipyretic drugs during the visit at which the child was immunized. Ninety-seven percent (80/82) of these respondents indicated that they recommended acetaminophen whenever discussing antipyretic therapy with parents of young children.

Based on their responses, pediatricians could be categorized into three groups: those who recommended prophylactic antipyretic therapy to all vaccine recipients, those who recommended antipyretic therapy to vaccine recipients only if and when the child became febrile, and those who gave no specific recommendations. Thirty-two percent (26/82) routinely recommended the use of prophylactic antipyretic therapy to all children following immunization, either by giving a dose in the office (2 of 82) or advising the use of prophylactic antipyretic therapy at home (24 of 82). Sixty-six percent (54/82) reported recommending antipyretic therapy at home only if the child became febrile, and 3% (2/82) did not give advice concerning antipyretic therapy.

These approaches to antipyresis were altered by some pediatricians depending on whether the child had experienced fever following a previous dose of vaccine. In counseling parents of children who had a febrile reaction to a previous dose of vaccine, 57% (47/82) of the respondents indicated that they would recommend the use of prophylactic antipyretic therapy with a subsequent dose of vaccine. Eighteen reported that in such cases they administered a dose in the office and 29 reported that they advised the use of prophylactic antipyretic therapy at home. Forty percent (33/82) replied that they recommended antipyretic therapy at home only if the child became febrile. The 2 who did not advise the use of antipyretics did not change their approach even if the child had a febrile reaction to a previous dose of vaccine.

Comment.—Our results indicate that among pediatricians surveyed, one third recommended the use of prophylactic antipyretic therapy to all children receiving DTP immunizations. Moreover, for the child who had a previous febrile reaction to DTP vaccine, 57% of the physicians recommended prophylactic antipyretic therapy. Thus, even prior to the publication of data supporting their efficacy, the use of antipyretic drugs following DTP was widely encouraged by the pediatricians in Rhode Island.

Of course, respondents to the questionnaire were anonymous, and the validity of the results depended on the candid responses of those surveyed. Also, responses to our survey reflect the pediatricians' perception of the advice they give to parents. We did not survey parents about the pediatricians' actual practices, nor did we directly observe pediatricians, office staff, or parents. Our sample included only pediatricians. We did not survey family practitioners, general practitioners, or nurse practitioners.

This survey sought to examine the prevalence of a common pediatric practice of unsubstantiated benefit. In light of recent documentation of the efficacy of acetaminophen in preventing febrile reactions to DTP immunizations, we plan to survey this group of practitioners again to assess the changes in practice that may have since been made. Such changes may

be fewer than would otherwise be expected, as our findings indicate that the recommendation of prophylactic antipyretic therapy in conjunction with immunization was already widespread.

PATRICIA J. FLANAGAN, MD
ANTHONY J. ALARIO, MD
JOHN S. O'SHEA, MD
GEORGES PETER, MD
Department of Pediatrics
Rhode Island Hospital
and Brown University
593 Eddy St
Providence, RI 02903

1. Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclar KCR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics.* 1981;68:650-660.

2. Ipp M, Gold R, Greenberg S, et al. Acetaminophen prophylaxis of adverse reactions following vaccination of infants with diphtheria-pertussis-tetanus toxoids-polio vaccine. *Pediatr Infect Dis J.* 1987;6:721-725.

3. Lewis K, Cherry JD, Sache MH, et al. The effect of prophylactic acetaminophen administration on reactions to DTP vaccination. *AJDC.* 1988;142:62-65.

Adolescents' Knowledge and Beliefs About AIDS: Did the Government Brochure Help?

Sir.—The US government distributed a brochure, "Understanding AIDS,"[1] to every household in the country in the spring of 1988. It described behaviors that place individuals at risk for human immunodeficiency virus infection. Urban adolescents are considered to be at high risk for this infection.[2] Moreover, research indicates that adolescents have inadequate knowledge and inaccurate beliefs about acquired immunodeficiency syndrome (AIDS).[3-5] The purpose of this study was to determine if urban adolescents who reported reading the government brochure would demonstrate higher levels of knowledge, less distorted beliefs, and lower levels of social anxiety about AIDS compared with adolescents who had not read the brochure.

Materials and Methods.—A total of 177 students attending a Cleveland, Ohio, public high school were asked to complete questionnaires in their social studies, health, and home economics classes in June 1988, 1 to 2 weeks following delivery of the AIDS brochure to local households. The questionnaire included four sections: demographic data, AIDS knowledge, AIDS beliefs, and anxiety about AIDS. It was approved by Cleveland Metropolitan General Hospital's Committee on Investigation in Humans, the parent committee at the school where the study took place, and the school's principal. Students were informed that participation was voluntary.

The knowledge scale included 22 items addressing current knowledge about AIDS, to which subjects responded "true," "false," or "don't know." Knowledge scores were computed by summing across all correct responses (potential range, 0 to 22). The beliefs scale was composed of 22 items corresponding directly to the knowledge questions. Subjects responded to each statement on a five-point Likert-type scale that ranged from 0 ("don't believe at all") to 4 ("believe completely"). Beliefs scores, computed by summing across items, had a potential range of 0 (beliefs completely consistent with current knowledge about AIDS) to 88 (beliefs completely contrary to current knowledge).

The social anxiety scale included six items that measured subjects' willingness to interact with someone who had AIDS. Responses of "yes," "not sure," and "no" were assigned values of 0, 1, and 2, respectively. Social anxiety scores, computed by summing across items, had a potential range of 0 (no anxiety) to 12 (very high anxiety).

Subjects were included in the analysis if they completed at least 20 of the 22 items in each of the knowledge and beliefs scales and all social anxiety questions. If only one or two values were missing in the knowledge or beliefs sections, the mean value of the remaining items was substituted. Of the 177 subjects, 145 returned questionnaires that met these criteria.

The subjects' mean age was 17 years (range, 13 to 19 years) and 19% were male. Eighty-three percent of the subjects were black, 11% were white, and 6% were from other ethnic groups. Forty-nine subjects (34%) reported having read "Understanding AIDS," while 96 (66%) said that they had not read the brochure. These two groups did not differ significantly by age and reported scholastic achievement (based on t tests), or by gender and race (based on χ^2 tests).

Results.—MANOVA was used to compare those students who reported reading the AIDS brochure with those who did not, using the knowledge, beliefs, and social anxiety measures as dependent variables. Results of the MANOVA and the univariate F tests were nonsignificant, indicating that the two groups did not differ with respect to their knowledge, beliefs, and anxiety about AIDS (Table).

Knowledge, Beliefs, and Social Anxiety Scores and Univariate F Values

Variables	Read Brochure (n=49)	Did Not Read Brochure (n=96)	F Value*
Mean knowledge score	17.17	16.26	2.0
Mean beliefs score	18.92	19.56	0.2
Mean social anxiety score	5.31	4.62	0.7

*$P>.15$.

Comment.—Although pretest measures were not gathered in this study, the findings suggest that the brochure, "Understanding AIDS," neither increased knowledge nor decreased belief distortion and social anxiety about AIDS in adolescents attending an urban high school. Nearly all of the surveyed students knew about high-risk behaviors. For example, 99% knew that sharing a needle with a drug user constitutes a high-risk activity. However, students were more confused about low-risk behaviors. For instance, only 50% knew that donating blood is not risky.

Written materials disseminated as a mass mailing to households did not appear effective in reaching inner-city adolescents, even though this strategy might successfully have reached adults. Our study's findings demonstrate the importance of designing interventions to meet the needs of particular groups. It may be important, for example, for school systems to develop approaches that are tailor-made for their students and not rely on information that might be more appropriate for a general adult audience.

Curricula designed for adolescents will need careful evaluation to determine whether they can influence attitudes, increase knowledge, and modify behaviors that place adolescents at risk for acquiring human immunodeficiency virus infection.

GREGORY D. ZIMET, PHD
TRINA M. ANGLIN, MD, PHD
RINA LAZEBNIK, MD
DEBRA BUNCH, MD
PAUL WILLIAMS, MD
DANIEL P. KROWCHUK, MD
Department of Pediatrics
Case Western Reserve University
School of Medicine
Cleveland Metropolitan General
Hospital
3395 Scranton Rd
Cleveland, OH 44109

1. Koop CE. *Understanding AIDS*. Atlanta, Ga: Centers for Disease Control; 1988. US Dept of Health and Human Services publication HHS-88-8404.
2. Hein K. AIDS in adolescents: a rationale for concern. *NY State J Med*. 1987;87:290-295.
3. Brown LK, Fritz GK. Children's knowledge and attitudes about AIDS. *J Am Acad Child Adolesc Psychiatry*. 1988;27:504-508.
4. DiClemente RJ, Boyer CB, Morales ES. Minorities and AIDS: knowledge, attitudes, and misconceptions among black and Latino adolescents. *Am J Public Health*. 1988;78:55-57.
5. Helgerson SD, Petersen LR, AIDS Education Study Group. Acquired immunodeficiency syndrome and secondary school students: their knowledge is limited and they want to learn more. *Pediatrics*. 1988;81:350-355.

Interactions of Alcohol and Nutrition

Sir:—Friedman et al[1] suggest three different mechanisms to explain the elevated serum iron concentrations found in adolescent alcohol users, the most likely being an enhanced absorption of dietary iron. Alcohol abuse can affect the nutrient status of an individual, eg, by reducing total food intake because of the high energy content of ethanol and by interfering with the absorption and metabolism of specific nutrients.[2,3]

The existence of an alcohol–trace metal interaction is known. Alcohol consumption in humans and animals reduces tissue zinc levels because of the diminished intake and intestinal absorption, for example, as well as the increased urinary excretion, of the trace element.[3-8] Severe zinc deficiency in rats is accompanied by a striking elevation of iron concentrations in serum, liver, and other body tissues.[9] Rogers et al[9] have suggested that this effect could explain increased iron absorption and/or increased binding of iron to ferritin in zinc-deficient animals.

Although the effect of zinc deficiency on iron levels in humans has not been documented, the findings of Friedman et al may, in part, be related to a secondary zinc deficiency, which could contribute to the elevated serum iron concentrations. Interestingly, in the study of Friedman et al, alcohol had a greater effect on iron metabolism in male than in female adolescents. Males are generally more susceptible to nutritional deprivation than females, and apparently this is also true for zinc deprivation.[10]

We suggest that an evaluation of nutritional status, particularly in respect to zinc, be performed in similar studies to assess the contribution of different nutrient interactions to the effects of alcohol consumption.

Roque M. C. da Cunha Ferreira, MD
Department of Pediatrics
Hospital de Santa Maria
Universidade de Lisboa
Av Egas Moniz
1699 Lisboa Codex
Portugal

1. Friedman IM, Kraemer HC, Mendoza FS, et al: Elevated serum iron concentrations in adolescent alcohol users. *AJDC* 1988;142:156-159.
2. Lieber CS: Interactions of alcohol and nutrition: Introduction to a symposium. *Alcoholism* 1983;7:2-4.
3. Mills PR, Shankin A, Anthony RS, et al: Assessment of nutritional status and in vivo immune responses in alcoholic liver disease. *Am J Clin Nutr* 1983;38:849-859.
4. Prasad AS, Oberleas D, Halsted JA: Determination of zinc in biological fluids by atomic absorption spectrophotometry in normal and cirrhotic subjects. *J Lab Clin Med* 1965;66:508-516.
5. Flynn A, Miller SI, Martier S, et al: Zinc status of pregnant alcoholic women: A determinant of fetal outcome. *Lancet* 1981;1:572-575.
6. McClain CJ, Su LC: Zinc deficiency in the alcoholic: A review. *Alcoholism* 1983;7:5-10.
7. Dinsmore WW, Callender ME, Macmaster D, et al: The absorption of zinc from a standardized meal in alcoholics and in normal volunteers. *Am J Clin Nutr* 1985;42:688-693.
8. Antonson DL, Vanderhof JA: Effect of chronic ethanol ingestion on zinc absorption in rat small intestine. *Dig Dis Sci* 1983;28:604-608.
9. Rogers JM, Keen CL, Hurley LS: Zinc deficiency in pregnant Long-Evans hooded rats: Teratogenicity and tissue trace elements. *Teratology* 1985;31:89-100.
10. Golub MS, Gershwin ME, Hurley LS, et al: Studies of marginal zinc deprivation in rhesus monkeys: IV. Growth of infants in the first year. *Am J Clin Nutr* 1984;40:1192-1202.

Tack Up a Warning on TAC

Sir:—We would like to bring to the attention of your readers adverse reports on TAC, an anesthetic mixture of 0.5% tetracaine hydrochloride, 1:2000 adrenaline, and 11.8% cocaine hydrochloride, used for topical application.

Originally, Pryor et al[1] reported the effectiveness of this preparation in 1980, and in 1988, Bonadio and Wagner[2] reported its safe and effective use for anesthetizing minor lacerations of the skin in children.

Since the publication of these articles there have been three reports of serious adverse reactions in the literature. A 7-month-old female infant, following mucosal lip application of TAC before suturing, was found dead in her crib three hours later. Her plasma cocaine concentration was 11.9 mg/L and her blood tetracaine concentration was 1 mg/L.[3] A second report involved a 5-year-old boy who, following buccal application of TAC before suturing, developed a seizure ten minutes after the application.[4] The third report involved a 15-month-old female infant who received 10 mL of TAC applied over burn areas of the face, chest, abdomen, and upper extremities. A generalized seizure was noted two to three minutes after application.[5]

In addition, we have recently received a report from a physician in Virginia of a case of palatine mucosal application of TAC before suturing in a 6-year-old boy resulting in convulsions within ten minutes. This physician also recalled a 6-month-old patient with a similar reaction after TAC mucosal application six months earlier. He is doing a survey of emergency departments using this agent and has been encouraged to report his two cases to the Food and Drug Administration and possibly to publish them.

According to the sixth edition of *Drug Evaluations*[6] published by the American Medical Association and the seventh edition of *The Pharmacological Basis of Therapeutics*,[7] cocaine concentration on the mucosa greater than 4% is not advisable, and the moistening of cocaine powder with epinephrine solution to form "cocaine mud" for use on the nasal mucosa is dangerous.

We would like to recommend that this solution not be used on mucosal or denuded surfaces and that authoritative bodies such as the Food and Drug Administration and/or the Committee on Drugs of the American Academy of Pediatrics evaluate the data on this combination and issue a statement about its use. No specific manufacturer is involved because the combination is prepared using the ingredients listed.

Howard C. Mofenson, MD
Thomas R. Caraccio, PharmD
Long Island Regional
Poison Control Center
Nassau County Medical Center
2201 Hempstead Turnpike
East Meadow, NY 11554

1. Pryor GJ, Kilpatrick WR, Opp DR: Local anesthetic for minor lacerations: Topical TAC vs lidocaine infiltration. *Ann Emerg Med* 1980;9:568-571.
2. Bonadio WA, Wagner V: Efficacy of TAC topical anesthetic for repair of pediatric lacerations. *AJDC* 1988;142:203-205.
3. Dailey RH: Fatality secondary to the misuse of TAC solution. *Ann Emerg Med* 1988;17:159-160.
4. Daya MR, Burtan BT, Scleiss MR, et al:

Recurrent seizures following mucosal application of TAC. *Ann Emerg Med* 1988;17:646-648.

5. Wehner D, Hamilton GC: Seizures following topical application of local anesthetics to burn patients. *Ann Emerg Med* 1984;13:456-458.

6. American Medical Association: *Drug Evaluations*, ed 6. Chicago, American Medical Association, 1986, p 283.

7. Gillman AG, Goodman LS, Rall TW, et al: *The Pharmacological Basis of Therapeutics*, ed 7. New York, Macmillan Publishing Co Inc, 1985, p 309.

Telephone Etiquette: The Telephone, One of the Physician's Most Necessary and, at Times, Most Hated Devices

Sir.—My teacher, friend, and most respected colleague, the late Lloyd E. Harris, MD, a Mayo Clinic pediatrician, tried to teach me, among many other things, the first lesson about telephone etiquette for physicians, which is: "*Do not call your colleagues unless there is an emergency or you need information right this minute.*"

Dr Harris found interruptions by telephone calls almost rude. His main reason for advising against the liberal use of the telephone was obvious: In our daily practice, every telephone call reaching us through our modern paging devices without delay is always an unscheduled interruption. When we are seeing patients we might be stopped at a crucial moment of history taking, in the process of taking a blood pressure, or, worse yet, when giving some bad news. Furthermore, the patient in the room becomes witness to information that might be confidential or to one side of a conversation that can be easily misinterpreted. In our large group practice, the ease of communication has always had a high priority. How can we find an acceptable compromise?

Abraham Bergman, MD,[1] pointed out recently that a junior pediatric resident receives an average of 50 telephone calls a day. He wondered about the necessity of being able to call junior residents and suggested that they should be freed from the pager. This may seem a very radical solution initially, but when we think of the frequency of nonemergency communications, we might join the Bergman movement. No one will question the need to call someone in a true emergency. It seems obvious, in line with Dr Bergman's suggestion, to have one person on call for such situations. However, these must not be calls for the prescription of acetaminophen for a febrile child or to write an order for a pass.

Here are some suggestions:

1. Before you call a colleague, ask yourself whether there is an immediate need or whether you can send a note or notify a secretary or other person responsible for appointments. When you do need to contact a physician by telephone, apologize for the interruption and *be brief*. Acknowledge that you are aware of your imposition and will not abuse the privilege.

The surgeon who calls the internist about the findings at the time of an operation may think that this is a polite thing to do. Why shouldn't the internist wait until the surgical report comes to his or her desk? There are exceptions for emergency situations, of course.

2. Administrative matters can usually wait until the next meeting. Do not hesitate to contribute agenda items by writing a note, but do not call.

3. Consider having one person in the hospital on call for true emergencies; this approach is best for a pool of various services. This will need to be preceded by a massive reeducation effort. All nonemergency requests should be channeled to a ward secretary who can bring these matters to the attention of the resident on the floor at regularly scheduled times.

4. Pagers with a system allowing a code for true emergencies or a code to call back at one's convenience should be installed. All new pagers should have two specific capabilities: (*a*) to beep or vibrate so that the wearer of the pager does not disturb his or her colleagues and (*b*) display messages or telephone numbers from the person who is paging.

5. When you dismiss a patient to return to the primary physician, hand the patient a brief note with instructions for immediate care, and then follow up the note with a detailed letter rather than a telephone call. Again, problematic follow-up situations will require a telephone call. In the referral letter to the primary physician, include the time(s) when you can best be reached by telephone for further clarification of items in the letter and for other general questions.

6. Parents or patients need to be encouraged to write for advice regarding nonemergency situations, or an hour for telephoning should be established if the type of practice warrants such an approach (for example, the pediatric allergist).

7. A nonmedical person answering your telephone calls should have the maximal amount of information as to how you would like your telephone calls handled. There is a need to screen calls.

8. If financial advisors, stockbrokers, or insurance agents habitually call you at inconvenient times, obtain their home telephone numbers and ask them for information at 3 AM. They may get the hint.

GUNNAR B. STICKLER, MD
Mayo Clinic and Mayo Foundation
Rochester, MN 55905

The comments and additions made by Bruce Z. Morgenstern, MD, are most appreciated.

1. Bergman AB. Resident stress. *Pediatrics* 1988;82:260-263.

Prolonged Intravenous Infusions

Sir.—We read with interest the article by Shulman et al[1] in the August issue of *AJDC* and herein report our experience with 45 patients with cystic fibrosis in whom a total of 66 catheters were placed. Patients with cystic fibrosis are similar to patients in the study by Shulman and colleagues in that they also frequently require long-term intravenous therapy.[2-7] Our use of a peripherally inserted central catheter for administering antibiotics and supplemental alimentation intravenously has certain advantages.

Patients and Methods.—The patients' ages ranged from 7 to 45 years and their weights ranged from 22 to 65 kg. Our experience began with 23 patients in whom 38 catheters were placed.[2] The polyvinyl-chloride catheters were placed in the basilic or cephalic vein for a mean duration of 15.4 days (range, 5 to 49 days). An 86% success rate was obtained. No major complications such as sepsis, catheter or clot embolism, pneumothorax, vascular perforation, or hemorrhage occurred, although 11% of the patients required premature removal for minor complications such as clot occlusion and cracked catheters.

We have extended this experience to another 22 patients in whom we placed 28 4-0F Silastic catheters (Cook, Bloomington, Ind, CPICS-401J). These were placed by a modified Seldinger technique. A needle was placed percutaneously into the basilic vein in the antecubital fossa. A guide wire was then threaded through the needle. The needle was removed and an introducer was inserted over the wire. The introducer was then removed and a peel-away sheath was placed over the wire. The guide wire was then removed and a catheter with a stylette was placed through the sheath. The catheter was premeasured and cut under full sterile precautions for each patient. The measurement tracks the vein

from the antecubital fossa, up the medial surface of the arm to the axilla, across to the suprasternal notch, and then down to the base of the manubrium. The catheter was threaded into the superior vena cava with the patient's head turned down and toward the access site, discouraging internal jugular placement. If difficulty was encountered passing the catheter through the axilla, the patient was asked to perform several maximal inspiratory efforts, holding each one. After the third inspiration, the catheter was floated during expiration, with improved venous return. A Valsalva manuever was not encouraged. The stylette and sheath were withdrawn and placement was checked by a chest roentgenogram.

Results.—The mean duration of catheter placement was 14.5 days (range, 8 to 115 days) as catheters were used for intravenous administration of antibiotics and supplemental alimentation for a total of 406 patient-days. Six (27%) of these patients had two or more catheters placed, with an overall success rate of 90% for placement on the first attempt.

The catheter used for 115 days was designed with a Dacron sleeve and was tunneled subcutaneously. No major complications such as sepsis, catheter or clot embolism, pneumothorax, vascular perforation, or hemorrhage occurred. Only 1 (3%) of 28 catheters was removed prematurely after 9 days because of clot occlusion. Three (12%) episodes of local phlebitis were treated symptomatically, without shortening the duration of catheter treatment.

Four patients underwent attempted fluoroscopic catheterization and venograms of both arms. The venograms revealed partial irregular obstructive sclerosis of segments of the basilic, cephalic, and axillary veins that precluded catheterization. All four patients had undergone previous catheterizations with polyvinylchloride and polyethylene catheters. We have not had this problem with silicone catheters.

Comment.—Our experience continues to show that peripherally inserted central silicone catheters are safe, effective, and well tolerated by patients with cystic fibrosis of almost all ages. The basilic vein approach provides a successful alternative when confronted with the recalcitrant problem of repeated courses of long-term intravenous administration of antibiotics and supplemental nutrition.

JEFFREY B. SUSSMANE, MD
Miami Children's Hospital
6125 SW 31st St
Miami, FL 33155

1. Shulman RJ, O'Brian Smith E, Rahman S, Gardner P, Reed T, Mahoney D. Single- vs double-lumen central venous catheters in pediatric oncology patients. *AJDC*. 1988;142:893-895.
2. Zanni R, Shutack J, Schuler P, Christie D, Holsclaw D. Peripherally inserted central venous catheters for treatment of cystic fibrosis. *Pediatr Pulmonol*. 1985;1:328-332.
3. Dietrich K, Lobas J. Use of a single silastic IV catheter for CF pulmonary exacerbations. *Pediatr Pulmonol*. 1988;4:181-184.
4. Winter R, George RJD, Deacock SJ, Shee CD. Self-administered home IV antibiotic therapy in bronchiectasis and adult CF. *Lancet*. 1984;1:1338-1339.
5. Pollack P, Kadden M, Byrne W, Fonkalsrud E, Ament M. 100 patient years' experience with the Broviac Silastic catheter for central venous nutrition. *JPEN*. 1981;5:32-36.
6. Hodder S, Stern R. Safety of long duration IV heparin-lock needles for CF patients. *J Pediatr*. 1981;99:312-314.
7. Rucker R, Harrison G. Outpatient IV medications in the management of CF. *Pediatrics*. 1974;54:358-360.

In Reply.—I am not certain of Dr Sussmane's meaning when he writes that the use of a peripherally inserted central catheter has certain advantages. I assume that he means advantages over traditional, surgically placed catheters, such as those used in our study. The two methods do not seem comparable for at least two reasons. First, surgically implanted catheters are intended for long-term therapy. The mean number of catheter-days in our patients was 10-fold greater than that in Dr Sussmane's series. Second, the youngest patient in Dr Sussmane's group was 7 years old, compared with a mean age of 2.5 years in the single-lumen group in our study. The percutaneous technique he describes is similar to that which we and others have reported for use in premature infants.[1,2] This technique certainly may facilitate short-term venous access. Nevertheless, I strongly urge that retrospective and, ideally, prospective, randomized studies be performed for the comparison of any new catheter technique with standard methods of catheterization, so that results can be evaluated critically.

ROBERT J. SHULMAN, MD
Baylor College of Medicine
Department of Pediatrics
Section of Nutrition
6608 Fannin, Suite 601
Houston, TX 77030

1. Shulman RJ, Pokorny WJ, Martin CG, Petitt R, Baldaia L, Roney D. Comparison of percutaneous and surgical placement of central venous cathers in neonates. *J Pediatr Surg*. 1986;21:348-350.
2. Dolcourt JL, Bose CL. Percutaneous insertion of silastic central venous catheters in newborn infants. *Pediatrics*. 1982;70:484-486.

Research During Residency

Sir.—I applaud the comments of Stiehm[1] in his editorial in the December 1988 issue of *AJDC* calling for a greater emphasis on research in both medical school and pediatric residency training. However, Stiehm implied that no residency program currently has such a requirement and that only one is implementing it. At the Children's Memorial Hospital, Chicago, Ill, we require that each resident complete a research project as a criterion for fulfilling the requirements for residency training. This requirement was initially implemented in the mid-1970s and persists to this time. It has proved to be a most successful component of our training program, with which over 150 research projects have been performed, completed, and presented to the faculty at the end of the third year of residency training. Although not the goal of this requirement, nearly one third of these projects have been published in the medical literature.

Approximately one half of our residents enter primary pediatric practice on completion of their training, and some of them continue to participate in some form of research in that setting. A recently published article about our experience with our Pediatric Practice Research Group describes this type of involvement.[2]

We continue to be exceptionally proud of our residents and the research they conduct during their training, and believe that our experience corroborates the perspectives outlined in Stiehm's editorial.

ROBERT J. WINTER, MD
Department of Pediatrics
Children's Memorial Hospital
2300 Children's Plaza
Chicago, IL 60614

1. Stiehm ER. Some of my best clinical pediatricians are researchers. *AJDC*. 1988;142:1283.
2. Christoffel KK, Binns HJ, Stockman JA III, et al. Practice based research: opportunities and obstacles. *Pediatrics*. 1988;82:399-409.

Prolactinoma in an Adolescent Girl: Unusual Response to Bromocriptine Therapy

Sir.—Although pituitary tumors have been reported in young children,[1] prolactinoma in young girls is rare. The youngest described patient, to my knowledge, was a 13-year-old girl.[2] With bromocriptine mesylate therapy, the symptoms of patients with prolactinoma improve and the prolactin level

normalizes or is greatly reduced.[2-4] Herein, I describe another adolescent girl with prolactinoma, who showed a dissociation of response to bromocriptine, resumption of menses and cessation of galactorrhea, and continued elevation of prolactin levels.

Patient Report.—A 15-year-old black girl with cessation of menses for 1 year and galactorrhea for 6 months was referred to the pediatric endocrine clinic of the Walter Reed Army Medical Center, Washington DC, on July 31, 1979. Born July 12, 1964, her growth and development had been unremarkable. Menarche occurred at the age of 13 years (July 1977). Regular menses continued until December 1977 when it became scanty and infrequent and then stopped in July 1978 (at age 14 years). Milk secretion from both breasts was noted early in 1979 (at age 14.5 years). The secretion was intermittent and most noticeable after a hot shower.

History.—History of head injury, meningitis, encephalitis, or seizures was absent. The patient denied taking contraceptives, tranquilizers, or a drug likely to affect menses or produce lactation. She lacked libido and was not sexually active. The family history was unremarkable. The mother had no menstrual problems.

Physical Examination.—The physical examination revealed a seemingly normal, obese, black, 15-year-old girl, 168 cm tall, weighing 60.6 kg. Blood pressure was 116/47 mm Hg and the pulse rate was 76 beats per minute. Pupils were equal in size and reactive to light and accommodation. Ocular movements were full and field of vision and fundi were normal, as were findings of a neurological examination. Heart sounds were normal, and no bruits were heard. Lungs were clear to percussion and auscultation. A skin and musculoskeletal examination revealed no abnormality. Her breasts were pendulous, nipples were normal, and milk discharge was noted on palpation.

The patient's abdomen was soft, and the liver and spleen were not palpable. Facial hair was absent, and pubic hair was at Tanner stage IV. Pelvic examination revealed normal external genitalia and clitoris and a normally palpable midline uterus, and the vaginal orifice admitted one finger and was virginal. The cervix was mildly red, and no unusual discharge was noted. Rectal examination findings were normal.

Complete blood cell count and sequential multiple analyzer-20 and thyroid function test results (thyroxine, 118 nmol/L; triiodothyronine uptake, 0.44; free thyroxine index, 53 pmol/L; and thyrotropin, 3.7 mU/L) were normal. Her endocrine responses (Table) of growth hormone, corticotropin and cortisol, and thyrotropin to various stimuli were normal. Prolactin levels following bromocriptine mesylate challenge did not change significantly (from a basal level of 112.4 μg/L, the prolactin reached a nadir of 96.4 μg/L at 6 hours and rose to 107.6 μg/L 8 hours after ingestion of the drug). The diagnosis of prolactinoma was based on the elevated prolactin level (normal, 1.3 to 15.6 μg/L), which did not change on challenge with thyrotropin releasing hormone or chlorpromazine hydrochloride.[5] The prolactin values were 372 μg/L and 252 μg/L at 60 and 90 minutes, respectively, after ingestion of chlorpromazine (the basal level was 240 μg/L). After a dopamine infusion (4 μg/kg per minute), the prolactin level declined from 412 μg/L before the infusion to 97 μg/L at 180 minutes after the infusion, but rose again to 445 μg/L at 240 minutes after the infusion. This represents inadequate suppression of prolactin for normal female patients.[6] A sellar mass was documented on computed tomography of her head, and a mass in the sellar area was removed. The pathologic findings were characteristic of prolactinoma. A repeated thyrotropin releasing hormone test after surgery revealed a persistence of normal thyrotropin response and no change in the raised basal prolactin level. Bromocriptine mesylate therapy, begun in December 1979 in doses of 5 mg/d, was gradually increased to 10 mg/d during the next month. The galactorrhea decreased, but amenorrhea persisted until the dose of bromocriptine was increased to 20 mg/d on April 8, 1980. Galactorrhea ceased, and menses restarted on April 14, 1980. Menses became regular and stable, and lactation did not recur. During a transient serum sickness–type illness in early 1981, her menses became scanty, requiring an increase in the dose of bromocriptine mesylate to 25 mg/d. Bromocriptine, in a dose of 15 to 25 mg/d, was continued until January 1984. Reducing the dosage or stopping bromocriptine therapy dosages led to cessation of menses. In June 1984, she was well and symptom free. The prolactin levels, measured repeatedly, remained elevated (>100 μg/L; normal, 1.3 to 15.6 μg/L). The prolactin levels were elevated even when the menses resumed and galactorrhea stopped. A sellar lesion, noted on computed tomography in 1979, was not clearly visible on computed tomography 1 year later. On July 10, 1984, a computed tomographic scan of the sella with coronal views showed a pituitary tumor with some erosion of the sella floor. The pituitary adenoma was resected twice by a transsphenoidal approach. The first operation was on August 21, 1984, and the second was on January 18, 1985. In August 1984, the preoperative and postoperative prolactin values were 300 μg/L and 90 μg/L, respectively. These values compare with the prolactin value of 278 μg/L in July 1979, before bromocriptine therapy, and a range of values between 33.6 μg/L (only one value was this low, the usual value being >100 μg/L) to 402.6 μg/L while receiving bromocriptine. On September 5, 1984, the prolactin value was still 90 μg/L. However, in October it rose to 527.4 μg/L. The level remained in this range, necessitating a second operation. Computed tomography of her head, however, did not show any significant change in the morphologic features of the sellar or parasellar region. Histologic findings were consistent with a pituitary macroadenoma containing prolactin-secreting cells (by immunofluorescence). Immediate preoperative and postoperative prolactin levels for the second operation are not available, but the prolactin level on February 11, 1985 (24 days after the operation), was 527 μg/L; the March and July 1985 values were reported as 396.2 μg/L and 256.8 μg/L, respectively. The patient tolerated these procedures well, did not develop diabetes insipidus or other evidence of hypopituitarism, and was not receiving hormone replacement therapy. She was taking a small dose (2.5 to 5 mg) of bromocriptine on an irregular basis. Her last menstrual period was in September 1985, but galactorrhea had not recurred. As of September 1988

Values After Challenge With Luteinizing Hormone–Releasing Hormone and Thyrotropin-Releasing Hormone, and Insulin Hypoglycemia Test*

Values	Time, min						
	0	15	30	45	60	90	120
Luteinizing hormone, U/L	18.9	...	87.9	...	88.1	77.9	68.8
Follicule-stimulating hormone, IU/L	21	...	40.3	...	33.5	44.6	52.7
Thyrotropin, mU/L	3	...	28.6	...	17.9	14.2	9
Prolactin, μg/L	347	...	322	...	285	312	350
Glucose, mmol/L	4.82	3.80	2.22	2.60	3.71	...	...
Growth hormone, μg/L	<1.1	2.4	4.5	15.3	24.7	...	...
Cortisol, mmol/L	280	...	210	...	580	...	...

*Luteinizing hormone–releasing hormone dose was 190 μg intramuscularly, 100 μg/m²; thyrotropin-releasing hormone dose was 200 μg intravenously; and insulin hypoglycemia test dose, 6 U intravenously, 0.075 U/kg.

(at age 24 years), about 10 years after onset of the symptoms, she was well, weighed about 77 kg, and was working as a data entry clerk. She had been taking 5 mg of bromocriptine daily for the last 12 months. Menses were regular, but galactorrhea occurred occasionally. It is apparent that after adenomectomy, a smaller dose of bromocriptine is required to control symptoms. Serum prolactin level in September 1988 was still elevated at 192 μg/L; fundi, field of vision, and visual acuity were normal. Magnetic resonance imaging of the brain demonstrated no expansion of the tumor.

Comment.—Although prolactinomas are the most common secretory tumors of the pituitary,[5] they are very rare in young adolescents.[7] Huseman et al[2] described a 13-year-old girl with prolactinoma whose condition, unlike that of the patient in this study, responded to bromocriptine therapy, with normalization of prolactin levels and abatement of symptoms.

Besides being one of the youngest female patients with prolactinoma described, our patient, while receiving bromocriptine, manifested persistent elevation of prolactin levels with symptomatic improvement. This response to bromocriptine is unusual, has been rarely reported, and is different from the normalized prolactin response to bromocriptine therapy reported by Huseman et al.[2] According to Spark,[3] after a single dose of bromocriptine serum, the prolactin level falls to the normal range in 95% of patients, and continued treatment sustains normoprolactinemia. Once normoprolactinemia is achieved and galactorrhea ceases, ovulatory menses return.

Resolution of pressure symptoms and endocrine symptoms, a decrease in tumor size, and normalization or marked reduction of prolactin levels are reported to occur with bromocriptine therapy.[4] The remarkable feature in our patient was restoration of menses without normalization or significant lowering of the serum prolactin level. Noncompliance was not likely, because after a bromocriptine challenge test, prolactin levels were elevated, and serum prolactin levels in random blood samples taken during hospitalization while the patient was receiving bromocriptine were raised. It is possible that the fraction of immunoreactive prolactin with a small biological effect was elevated and that the other fraction with a large effect was low. Reduction in the tumor mass may play a role in the resumption of menses and cessation of galactorrhea; however, this cannot be the entire explanation because symptomatic improvement occurred before surgery and while the patient was receiving bromocriptine. Furthermore, in the immediate postoperative period, the prolactin levels decreased but did not become normal. The drug also failed to normalize the prolactin levels. Whittaker et al[7] found increased levels of "big, big" prolactin fraction in hyperprolactinemic but fertile women. Big, big prolactin shows reduced receptor affinity. We did not measure various fractions of prolactin and therefore cannot eliminate this possibility. Aubourg et al,[8] in a study of 90 patients, found that after transsphenoidal adenomectomy, menses were restored in only one patient in whom the prolactin level was elevated (>45 μg/L; normal value, <30 μg/L). In a 47-year-old man, continuation of bromocriptine therapy was ineffective in sustaining normal levels of prolactin and decreasing the tumor growth.[9]

The patient in the present report and the patient in the report of Huseman et al[2] were obese; this may be an incidental finding, or the obesity and the disturbance in prolactin secretion may be related. Lala et al[10] observed a blunted prolactin mean and peak response to thyrotropin releasing hormone stimulation in prepubertal obese children of both sexes. The response was not correlated with the degree of obesity.

CHANDRA M. TIWARY,
MBBS, MA, MBA
Department of Pediatrics
Brooke Army Medical Center
Fort Sam Houston
San Antonio, TX 78234-6200

I am grateful to LTC Allan Glass, MC, USA, for encouraging me to report the case presented in this study, to MAJ Jennifer Nuovo, MC, USA, for providing me some of the follow-up data, and to Helen Smith for reviewing the manuscript.

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or expressing the views of the Department of the Army or the Department of Defense.

1. Richmond IL, Wilson CB. Pituitary adenomas in childhood and adolescence. *J Neurosurg.* 1978;49:163-168.
2. Huseman CA, Rizk G, Hahn F. Long-term bromocriptine treatment for prolactin-secreting macroadenoma. *AJDC.* 1986;140:1216-1217.
3. Spark RF. Hyperprolactinemia and hypoprolactinemia. In: Hare JW, ed. *Signs and Symptoms in Endocrine and Metabolic Diseases.* Philadelphia, Pa: JB Lippincott, 1986:41-50.
4. Chakera TMH, Khangure MS, Pullen P. Assessment by computed tomography of the response of pituitary macroadenomas to bromocriptine. *Clin Radiol.* 1985;36:223-226.
5. Daughday WH. The adenohypophysis. In: Williams RH, ed. *Textbook of Endocrinology.* 6th ed. Philadelphia, Pa: WB Saunders Co; 1981:105.
6. Talo D, Malarkey WB. Physiological concentrations of dopamine fail to suppress prolactin secretion in patients with idiopathic hyperprolactinemia or prolactinomas. *Am J Obstet Gynecol.* 1985;151:651-655.
7. Whittaker PG, Wilcox T, Lind T. Maintained fertility in a patient with hyperprolactinemia due to big, big prolactin. *J Clin Endocrinol Metab.* 1981;53:863-866.
8. Aubourg PR, Derome PJ, Peillon F, et al. Endocrine outcome after transsphenoidal adenomectomy for prolactinoma: prolactin levels and tumor size as predicting factors: *Surg Neurol.* 1980;14:141-143.
9. Breidahl HD, Topliss DJ, Pike JW. Failure to maintain reduction in size of a macroprolactinoma. *Br Med J.* 1983;287:451-452.
10. Lala VR, Ray A, Jamias P, et al. Prolactin and thyroid status in prepubertal children with mild to moderate obesity. *J Am Coll Nutr.* 1988; 7:361-366.

In Other AMA Journals

JAMA
Management of Varicella Exposure in a Neonatal Intensive Care Unit
S. V. Lipton, P. A. Brunell (*JAMA.* 1989;1782-1784)

First and second year Osteopathic Pediatric residency positions are available at Grandview Hospital in Dayton, Ohio. This is a didactic program with a wide and varied caseload. Opportunity for appointment to the attending staff at the completion of the training program is available. For further information please contact:

H. Lauren Vogel, D.O.
DME at Grandview Hospital
405 Grand Avenue
Dayton, OH 45405-4796
or (513) 226-3247

HAMAD MEDICAL CORPORATION is a 1,200 bed referral facility and is the main health establishment in the country with its modernly equipped facilities, invites qualified applicants for **NEONATOLOGY** positions at all levels. Our Pediatric Department consists of:
52 Neonatal Intensive Care Units
18 Ventilator Units
34 Step Down and Isolation Units
10,000 Deliveries in 1988

REQUIREMENTS:
Completed Pediatric and Neonatology Training
Post Training experience required for higher levels.

BENEFITS:
Attractive tax free salaries based on qualifications and experience.
Free furnished accommodation
Round trip air ticket
40-50 days annual paid leave
Contracts for 3 years renewable upon mutual agreement

HOW TO APPLY:
Qualified applicants should send complete C.V. with contact telephone number to:

ATTN: MEDICAL DIRECTOR
Hamad Medical Corporation
P.O. Box 3050
Doha, State of Qatar
Arabian Gulf

NEONATOLOGIST

New Hanover Memorial Hospital, located in beautiful, historic, oceanside Wilmington, North Carolina is seeking a board certified or board eligible neonatologist to join team of three. New Hanover Memorial Hospital is a 500 bed major referral hospital for southeastern North Carolina with graduate medical education programs affiliated with the University of North Carolina School of Medicine. Candidate will be eligible for academic appointment at UNC School of Medicine. Academic appointment and salary dependent on training and experience. Please submit curriculum vitae and references to:

Chairman,
Search Committee in Neonatology
Area Health Education Center
New Hanover Memorial Hospital
2131 South 17th Street
Wilmington, North Carolina 28402

The University of North Carolina at Chapel Hill is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

PEDIATRICIAN

Immediate opportunity to associate with five pediatricians in an accredited 70-doctor multispecialty group. Drawing area of 400,000. Modern hospital within five minutes of Clinic. Stimulating Big-10 university community of 110,000 with superb cultural advantages. Ideal for families. Medical school teaching affiliation if desired. Excellent initial guarantee and fringes with early associate status, subsequent income based exclusively on productivity. Subspecialty training in allergy desirable. Send CV to:

Ronald H. Deering, Sr., M.D.
Christie Clinic Association
101 W. University
Champaign, IL 61820

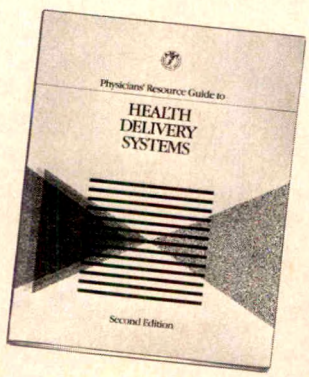
Break the language barrier of health delivery systems

Feel like you'll have to learn a new language to *really* understand health delivery systems? You're not alone. But there's a complete and easy-to-use book to enable you to break through the jargon...*Physicians' Resource Guide to Health Delivery Systems.*

Includes pro's and con's of HMOs, PPOs, IPAs; a list of government, consumer and other groups associated with HMOs; a glossary; abstracts; trends; historical data.

To order your copy, *phone toll free today.* MasterCard and Visa accepted.

1-800-621-8335



Measles—Los Angeles County, California, 1988

A PROVISIONAL TOTAL of 513 confirmed cases of measles was reported from Los Angeles County during 1988. The Los Angeles County cases represent 17.5% of all (2933) cases reported for the United States during this period and an incidence rate of 6.4 cases/100,000 persons—a risk 5.3 times higher than that in the rest of the United States (1.2/100,000).

Of 353 confirmed patients with known ages and onset from May 1 to December 31, 228 (64.6%) were less than 5 years of age. A total of 135 (38.2%) were less than 16 months of age (i.e., too young for routine vaccination), including 87 (24.6%) less than 12 months of age; 93 (26.3%) were 16 months to 4 years of age.

Preventability status was known for 353 (99.4%) of the cases; 150 (42.5%) of these were preventable, and 203 (57.5%) were considered programmatically nonpreventable.

The setting of transmission was known for 209 (58.9%) patients, of whom 120 (57.4%) had known household exposures to measles. Sixty-three (30.1%) acquired measles in medical settings.

One hundred twenty-two (34.4%) patients were hospitalized. Of the 355 patients, 60 (16.9%) had diarrhea, 37 (10.4%) had otitis media, 35 (9.9%) had pneumonia, three (0.8%) had encephalitis, and two (0.6%) had meningitis.

Two measles-associated deaths occurred for a reported death-to-case ratio of 5.6/1000 cases. One death occurred in an 8-month-old infant, the other in a 23-month-old unvaccinated child. Both patients had nosocomially acquired cases and were exposed to measles while hospitalized for other illnesses.

On July 21, the Los Angeles County Department of Health Services lowered the minimum age for measles vaccination to 12 months.

Reported by: G Lentini, P Heseltine, MD, Los Angeles County/Univ of Southern California Medical Center, Los Angeles; J Amling, E Evashwick, Childrens' Hospital, Los Angeles; E Smith, Kaiser-Bellflower Hospital, Bellflower; SR Waterman, MD, PD Frederick, MPH, County of Los Angeles Dept of Health Svcs; L Dales, MD, D Lyman, MD, State Epidemiologist, California Dept of Health Svcs. Div of Immunization, Center for Prevention Svcs, CDC (MMWR vol 38, No. 4).

Editorial Note: Measles transmission in preschool-aged children remains a major impediment to elimination of measles in the United States. Measles epidemiology in Los Angeles County is similar to that of other recent inner-city measles outbreaks among preschoolers in low socioeconomic groups in which most affected persons were unvaccinated. To improve vaccine coverage in high-risk children less than 15 months of age, the Immunization Practices Advisory Committee (ACIP) recently recommended that public health officials in areas with recurrent measles transmission lower the minimum age for routine vaccination to 9 months of age. Children vaccinated before their first birthday should receive single-antigen measles vaccine and be revaccinated with measles, mumps, and rubella vaccine (MMR) at 15 months of age. An alternate strategy is to lower the age for routine vaccination to 12 months using one dose of MMR.

Queens Boulevard Pedestrian Safety Project—New York City

TO ADDRESS the problem of pedestrian injuries, the Safety Division of the New York City Department of Transportation established an Urban Pedestrian Safety Strategy in 1985. The strategy called for the collection, mapping, and analysis of collision data to identify hazardous sites and develop interventions. The Queens Boulevard Pedestrian Safety Project, an example of the application of this strategy, focused on fatal injuries to pedestrians. For this project, 1980-1984 data were examined from investigation reports of a special police unit that responded within 1 hour to calls from local police precincts when a severe pedestrian injury occurred. If a pedestrian fatality had already occurred or the physician providing emergency medical care determined that the victim was not likely to survive, the investigators collected information about the injury circumstances, and persons involved. Using this information, the Department of Transportation identified factors associated with risk of pedestrian fatalities at Queens Boulevard and planned interventions to improve safety at this site.

Queens Boulevard is the widest street (175-225 feet) in New York City. More than 60,000 vehicles traverse its 12 traffic lanes daily. Spot mapping of 1980-1984 police data identified a geographic cluster of 22 deaths and 18 likely fatalities along a 2.5-mile length of the street. Age was known for 36 (90%) of the 40 injured pedestrians; pedestrians injured along Queens Boulevard were older than pedestrians injured in the entire city. All 20 fatally injured pedestrians for whom ages were known were greater than or equal to 60 years old.

Because many of the fatalities occurred in older pedestrians crossing the street, the following interventions

were implemented: 1) modification of stop light signals to increase pedestrian crossing time; 2) roadway markings to emphasize pedestrian crosswalks, traffic lanes, and the direction of traffic flow; 3) pedestrian signals on median islands; 4) oversized speed limit signs and increased police enforcement of the speed limit; and 5) safety education presentations at senior citizen centers. The estimated cost of these interventions was $150,000.

Based on the average daily motor vehicle traffic volume on the Queensboro Bridge, the average daily traffic volume on Queens Boulevard may have increased by 19% in the 2 years after the interventions when compared with traffic volume during the 5 years preceding the interventions. Despite these increases in volume, the annual occurrence of fatal and likely fatal pedestrian injuries decreased substantially after the interventions (43% and 86%, respectively). Citywide occurrence of fatal pedestrian injuries decreased by only 4% over the same period.

Reported by: R Retting, Safety Div, SI Schwartz, M Kulewicz, Safety Engineering, New York City Dept of Transportation; LT D Buhrmeister, Accident Investigation Squad, New York City Police Dept. Unintentional Injuries Section, Epidemiology Br, Div of Injury Epidemiology and Control, Center for Environmental Health and Injury Control, CDC (MMWR vol 38, No. 5).

Editorial Note: Despite a slight decline in the rate of pedestrian fatalities associated with motor vehicle collisions over the past decade, over 7000 such deaths still occur each year in the United States.[1] An estimated 80,000 nonfatal pedestrian injuries occurred during 1986.[2] Pedestrian fatalities accounted for an estimated 15% of all 1986 traffic fatalities and 23% of urban traffic fatalities.[3] Pedestrian deaths represent an even greater proportion of traffic fatalities in the most densely populated urban areas. In New York City, for example, 314 (52%) of 610 traffic fatalities in 1987 were among pedestrians.[4]

Motor vehicle traffic control traditionally has focused on optimization of traffic flow and, more recently, conservation of fuel. In general, safety concerns, particularly pedestrian safety, have received less emphasis. For example, to reduce fuel consumption, all states in the United States had adopted traffic laws allowing right turns on red lights by the end of the 1970s. These right turns, however, appear to have increased police-reported collision rates, particularly for elderly pedestrians in urban areas.[5] An additional impediment to intervention is the public perception of such injuries as "accidents"—unavoidable by-products of motor vehicle travel—rather than "injuries," for which preventive measures can be taken. Furthermore, there has been a tendency to blame pedestrian injury on pedestrian negligence,[6,7] yet drivers and environmental conditions play an important role and cannot be excluded from the injury prevention equation.[8]

The Queens Boulevard Pedestrian Safety Project demonstrates how focusing on injury prevention and incorporating resources not traditionally involved in public health can substantially improve safety with little effort or expense. Studies indicate that pedestrian injuries have their greatest impact on the very young, the very old, and the intoxicated.[3,6-13] By recognizing Queens Boulevard as a street segment with an unusually large number of pedestrian injuries and identifying the elderly as the primary population at risk, traffic engineers and others devised interventions focusing primarily on disabilities of vision and agility in the elderly. This project suggests that pedestrian injuries may be prevented with interventions involving engineering, enforcement, education, legislation, and zoning. With a multidisciplinary approach and safety as a priority, public health officials, traffic planners, law enforcement officials, and other public safety workers can continue to take steps to reduce fatalities on U.S. roads.

References

1. National Center for Health Statistics. Vital statistics mortality data, multiple cause of death detail (machine-readable public-use data file). Hyattsville, Maryland: US Department of Health and Human Services, Public Health Service (annual).

2. National Safety Council. Accident facts: 1987 edition. Chicago: National Safety Council, 1987.

3. National Highway Traffic Safety Administration. Fatal Accident Reporting System 1986. Washington, DC: US Department of Transportation, National Highway Traffic Safety Administration, 1988; DOT publication no. (HS)807-245.

4. New York City Department of Transportation. Traffic fatalities in New York City: 1987. New York: New York City Department of Transportation, Bureau of Planning and Research, 1988.

5. Zador P, Moshman J, Marcus L. Adoption of right turn on red: effects on crashes at signalized intersections. Accid Anal Prev 1982;14:219-34.

6. Solheim K. Pedestrian deaths in Oslo traffic accidents. Br Med J 1964;1:81-3.

7. McCarroll JR, Braunstein PW, Cooper W, et al. Fatal pedestrian automotive accidents. JAMA 1962;180:127-33.

8. Baker SP, Robertson LS, O'Neill B. Fatal pedestrian collisions: driver negligence. Am J Public Health 1974;64:318-25.

9. Allard R. Excess mortality from traffic accidents among elderly pedestrians living in the inner city. Am J Public Health 1982;72:853-4.

10. Baker SP. The man in the street: a tale of two cities (Commentary). Am J Public Health 1975;65:524-5.

11. Haddon W Jr, Valien R, McCarroll JR, Umberger CJ. A controlled investigation of the characteristics of adult pedestrians fatally injured by motor vehicles in Manhattan. J Chronic Dis 1961;14:655-78.

12. Mueller BA, Rivara FP, Bergman AB. Factors associated with pedestrian-vehicle collision injuries and fatalities. West J Med 1987;146:243-5.

13. Tanz RR, Christoffel KK. Pedestrian injury: the next motor vehicle injury challenge. Am J Dis Child 1985;139:1187-90.

In Other AMA Journals

JAMA

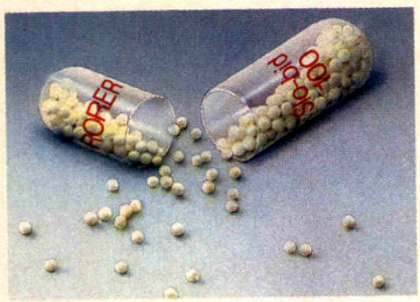
Temporal Patterns of Cocaine Use in Pregnancy

I. J. Chasnoff; D. R. Griffith; S. MacGregor; K. Dirkes; K. A. Burns (*JAMA*. 1989;261:1741-1744)

HIV Seroprevalence in Newborns in New York State

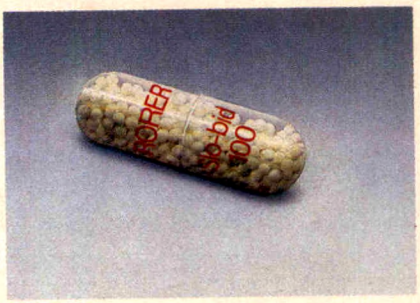
L. F. Novick; D. Berns; R. Stricof; R. Stevens; K. Pass; J. Wethers (*JAMA*. 1989;261:1745-1750)

Growing up on a steady theophylline is an open-and-shut case



Sprinkled

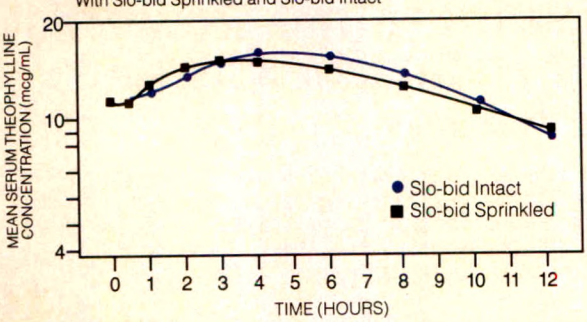
Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration[1]

Mean Serum Theophylline Concentration in 14 Children Dosed With Slo-bid Sprinkled and Slo-bid Intact



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.[2]

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in applesauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

In asthma and bronchitis

Slo-bid™ 12

(theophylline, anhydrous)

Nothing beats our system

From the makers of **Azmacort**™ (triamcinolone acetonide)

Please see next page for brief summary of prescribing information.

©1989 Rorer Pharmaceutical Corporation
Printed in U.S.A. FC#89-40 SB06189A 1/89

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

Slo-bid

(theophylline, anhydrous)
50 mg, 100 mg, 200 mg, and 300 mg

Gyrocaps®
Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 100 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 μg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 μg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 μg/mL.

Information for Patients:
The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:
Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Rifampin	Decreased serum theophylline levels

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromotography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C – Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness of Slo-bid Gyrocaps administered:
1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

50 mg – Clear (cap) and opaque white (body) capsule with 50 printed in red
100 mg – Clear capsule with 100 printed in red
200 mg – Opaque white (cap) and clear (body) capsule with 200 printed in red
300 mg – Opaque white capsule with 300 printed in red

Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0057-99) and in unit dose 10 x 10 (NDC 0075-0057-62). Slo-bid Gyrocaps 100 mg are available in bottles of 100 (NDC 0075-0100-00), bottles of 1000 (NDC 0075-0100-99) and in unit dose 10 x 10 (NDC 0075-0100-62). Slo-bid Gyrocaps 200 mg are available in bottles of 100 (NDC 0075-0200-00), bottles of 1000 (NDC 0075-0200-99) and in unit dose 10 x 10 (NDC 0075-0200-62), and Slo-bid Gyrocaps 300 mg are available in bottles of 100 (NDC 0075-0300-00), bottles of 1000 (NDC 0075-0300-99) and in unit dose 10 x 10 (NDC 0075-0300-62), and are manufactured by:

RORER PHARMACEUTICALS
a division of
Rorer Pharmaceutical Corporation
Fort Washington, PA, U.S.A. 19034

R O RORER E R

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

TURNER SYNDROME TREATMENT

The National Institutes of Health requests the cooperation of physicians in referring patients with Turner syndrome, age 4 to 11 years. Patients will be offered enrollment in a long-term treatment protocol to assess the effect of low-dose estrogen treatment and growth hormone treatment on adult height. Referring physicians will receive a complete summary of all evaluations, and patients will continue to be followed in conjunction with their referring physicians. Please write or telephone:

Dr. Gordon B. Cutler, Jr.
NIH, Building 10, Room 10N262
Bethesda, MD 20892
301-496-4686

or

Dr. Judith Levine Ross
Hahnemann University
Mail Stop 402
Broad and Vine Streets
Philadelphia, PA 19102
215-448-7710

Examine the Rewards of a CIGNA Career!

■ Pediatrics

As one of the nation's largest investor-owned health maintenance organizations, we realize the importance of skilled and dedicated physicians. This is why we are committed to taking good care of you! We provide:

- Scheduled working hours with paid vacation, paid malpractice insurance and the time and funding you will need for professional development
- Excellent benefits including health, life, pension and a 401K retirement savings plan
- Competitive salary structure

For confidential consideration, send your C.V. to **Carolyn Pabich, Dept. SS - Physician Recruitment, CIGNA Healthplan of Texas, Inc., P.O. Box 542588, Dallas, Texas 75354-2588, or call (214) 401-5303.**

CIGNA Healthplan of Texas, Inc.

CIGNA

Equal Opportunity Employer, M/F/V/H

Is Standard Practice in Pediatrics 'Standard'?

A Potential Lesson for Experts and Practitioners

In this issue of *AJDC*, Schunk and coworkers[1] present a concise study of the results of analysis of roentgenographic findings on ingestion of coins by children. Another study published in this issue takes a somewhat different viewpoint concerning the value of roentgenograms.[2] Both studies appear to be straightforward, but buried in the report by Schunk and colleagues[1] is a finding that startled some of our reviewers and our editorial staff. In a regional telephone survey of 65 practicing pediatricians, the responses demonstrated that 70% of physicians would *not* obtain a roentgenogram of a child who had ingested a coin and was asymptomatic. The study by Caravati et al[2] reinforces this view. However, our referees and editors alike believed that almost all sources of authoritative advice concerning coin ingestions recommend, as standard practice, the use of roentgenography to determine the placement of the ingested coin and to condition future action. In the face of this assumed "standard" the overwhelming number of physicians who would not adhere to it proved disturbing. The finding raises some generic issues: What is standard practice in a given clinical area? Who establishes the "national" standard? Are there regional variations? Is compliance assured by this process?

See also pp 546 and 549.

In many areas of practice, research and/or careful, documented clinical observation have resulted in sufficient data for most, if not all, pediatric practitioners to accept the notion that a standard of practice has been achieved. Physicians confronted with a specific clinical problem need to have some concept of this standard to practice "good" medicine, ie, diagnosis and treatment that meet the test of effectiveness for their patients. The specific example cited in the two reports in this issue, that of ingestion of coins, is a case in point. Observations in the past have appeared to demonstrate that the asymptomatic patient does not necessarily have a benign course after ingestion of the coin; mucosal erosion and impaction have been two of the complications identified in the study by Schunk et al[1] and in previous studies. Therefore, it would seem prudent to identify these radiopaque objects, and to remove them if they do not pass spontaneously. And yet, 45 of the 65 pediatricians surveyed would not have done so. Reinforcing this view are the observations in the study by Caravati et al.[2] Why is this so?

Standards are usually set by the publication of results and often are codified by experts in a given area in textbooks, manuals, advisory group recommendations, federal or other governmental regulation, or, in the worst case, by the outcome of litigation in a given jurisdiction. Experts, whether writing as authors in a textbook or manual, or acting as members of an advisory group (such as the Committee on Infectious Diseases of the Academy of Pediatrics), attempt to digest, analyze, and report on their evaluations of the known research or clinical observations. In areas where there is substantial agreement, these opinions take on the aura of authoritative judgment, and set the tone for the entire profession. These opinions are used by local peer-review committees, by hospital staff committees, by lawyers, judges, and juries, and by others as the prevailing standard in that clinical area. How else could one measure an individual physician's actions in that area, unless one can compare it with some near-universal opinion as to what is "correct," ie, to a national standard? Obviously, there are many areas in clinical practice that do not reach such unanimity or consensus as to what is correct; some allow for wide interpretation by the individual practitioner, and others for a narrower range of options, but still not a single course of action.

Why then is there not universal compliance to such standards, such as the one detailed by Schunk and colleagues?[1] There are many possible explanations. First, the individual practitioner may not know of the standard. This can result from practice having changed since he or she learned an approach to the problem, practice that is now "incorrect." In such an instance, the practitioner may not have "kept up" and therefore continues a previous practice that is no longer au courant. If this is the reason, then I can think of no greater argument for conscientious attention to continuing medical education in those areas that the practitioner encounters in his or her practice.

A second possible explanation is that the practitioner does not agree with the consensus. Fortunately, and unfortunately, medicine is still an entrepreneurial art and science. Physicians are thinking professionals and do not necessarily accept all conventional wisdom. This is fortunate in that it permits us to challenge and ultimately correct mistaken expert opinion. It is unfortunate in that it enables the individual to practice poor medicine solely on the premise that he or she does not agree with evidence, no matter how scientifically rigorous it is. Another aspect of disagreement with consensus is that a local expert or consultant may disagree with the

expert or experts who established the standard. The practitioner then may be faced with divergent views, one a presumed national standard and the other a respected local one. This divergence could present medicolegal problems. If one disagrees with a consensus, does documentation in the record suffice to justify the differing action? I do not know the answer to this question, but it and variations thereof could pose significant problems for the entrepreneurial practitioner.

A third possibility is that the individual practitioner knows of the standard but has misinterpreted it. This can occur because the method of presentation is confused or incomplete, ie, the recommendation is made in ambiguous terms or is unaccompanied by the reasoning behind it. In this instance it behooves the experts to examine their recommendations to ensure that they conform to clarity and explicitness and are supported by sufficient exploration of the basis for them.

A fourth possibility is that the assumed "standard" does not exist, or is not explicitly presented. After all, each of us is a product of our medical education, both in medical school and residency, and of our continuing education thereafter. Many of us have come to believe that we know the standards and that everyone agrees with us, such that any authoritative source would verify our own impressions. It is possible that this is not so, however we may wish it to be otherwise. The study by Caravati et al[2] suggests that conventional wisdom (as assumed by our referees and editors) is not necessarily true.

With these thoughts in mind, and thinking that any text would obviously demonstrate a standard recommendation, I examined the usual pediatric sources for the recommendation that roentgenograms should be obtained of children who ingested coins.[3-6] In one text, the description of the clinical manifestations is so mixed in character that the reader is not clear on what course of action should be followed for the asymptomatic child. Little mention is made of complications, should a roentgenogram not be obtained and the coin remain in the esophagus. In another source text, the discussion of coins is arrayed amid a general discussion of foreign bodies and it is difficult to determine what the standard of practice is for asymptomatic children who have ingested coins. Furthermore, statements are made that suggest that most esophageal foreign bodies pass uneventfully into the stomach, after which they cause no problems (this statement is inclusive of open safety pins). In yet a third text, the message is quite mixed, with a statement at the outset indicating that most foreign bodies pass through the alimentary tract "without difficulty," and later that esophagogastroscopy will permit removal of the majority of foreign bodies lodged in the esophagus or stomach. Nowhere in this account is mention made of a recommendation for roentgenography. Other accounts have similar problems.

I came away from this analysis somewhat dismayed. The departments of pediatrics and radiology that I have been associated with in the past 30 years have uniformly taught and expected that coin ingestion would be followed by roentgenographic examination and then by appropriate action. Indeed, this was the expectation in the report by Schunk and coworkers.[1] In sharp contrast, Caravati et al[2] reach an opposite conclusion. Furthermore, the textbooks we usually rely on to convey such information do not do so clearly, or in some cases do not do so at all. Thus, despite the assumption of the authors, our reviewers, and our editorial staff, and my assumption, that such information was readily available in clear-cut fashion, I have to conclude that in any of the peer-review or legal forums that I delineated earlier, one could not clearly establish that a standard of practice exists, or if it does, that it is conveyed to the reader in convincing fashion.

What remains is the assumption that a practitioner will not rely solely on standard textbooks, but will have read the literature himself or herself and will have kept abreast in that fashion. This is an unreasonable expectation in many situations, and especially in the current instance of coin ingestions. The references cited in the textbooks and in the articles published in this issue of *AJDC* are found in the otolaryngologic, emergency medicine, surgical, and radiologic literature, and are not extensively published in the pediatric journals. Some of the articles cited are in the usually inaccessible foreign literature. It is not reasonable to expect a busy practitioner to search these sources to determine the standard of care in coin ingestions.

What can be done? I hope that publication of these articles, including the "small" point of the survey in the article by Schunk et al[1] that demonstrated apparent noncompliance with a standard of practice, accompanied by the present editorial comment, will stimulate change. Those of us who are experts in a given area should be much more explicit in our writing, keeping in mind that the practitioner may look to our words for guidance. Furthermore, practitioners might benefit by knowing that their practices might not conform to some standard held by experts. They probably should seek counsel from experts to reexamine important issues in their practice, when they encounter an article that appears to contradict what they are doing. These are small steps taken against a much larger problem, but may help in its resolution.

VINCENT A. FULGINITI, MD
Editor, *AJDC*
Dean's Office
Room 1529
Tulane University
School of Medicine
1430 Tulane Ave.
New Orleans, LA 70112

References

1. Schunk JE, Corneli H, Bolte R. Pediatric coin ingestions: a prospective study of coin locations and symptoms. *AJDC*. 1989;143:546-548.
2. Caravati EM, Bennett DL, McElwee NE. Pediatric coin ingestion: a prospective study on the utility of routine roentgenograms. *AJDC*. 1989;143:549-551.
3. Behrman RE, Vaughn V III, Nelson W, eds. *Nelson Textbook of Pediatrics*. 13th ed. Philadelphia, Pa: WB Saunders Co; 1987.
4. Rudolph AM, Hoffman JIE, Axelrod S, eds. *Pediatrics*. 18th ed. Norwalk, Conn: Appleton & Lange; 1987.
5. Kempe CH, Silver HK, O'Brien D, Fulginiti V, eds. *Current Pediatric Diagnosis and Treatment*. Norwalk, Conn: Appleton & Lange; 1987.
6. Hoekelman R, Blatman S, Stanford B, Friedman SB, Nelson NN, Seidel H, eds. *Primary Pediatric Care*. St Louis, Mo: CV Mosby Co; 1987.

Dietary Advice

Responsibility for Monitoring

The report by Lifshitz and Moses[1] in this issue of *AJDC* demonstrates the potential problems accompanying well-intentioned pediatric advice without adequate follow-up. The particular data also deal with an important medical problem of our time for which we do not yet have rigorous or near-rigorous scientific data to guide our actions.

See also p 537.

The problem may be stated as pertaining to what measures should be taken in childhood to prevent coronary artery disease in adult life. The evidence of a close *association* of increased cholesterol levels (specifically, low-density lipoprotein [LDL] levels) with increased risk and incidence of coronary artery disease in adult life is strong. The evidence that fatty streaks in the aorta are sometimes found at the end of childhood is indisputable. That fatty streaks *may* progress to fibrous plaque, which in turn may progress to atheromatous lesions, is generally accepted. It is also known that fatty streaks and fibrous lesions need not progress and are even reversible in adult patients when LDL levels are lowered.

Strong evidence also exists that LDL (and the apparently beneficial high-density lipoprotein) levels are determined by both genetic and environmental influences. The genes determine the protein carriers of lipids and therefore the amounts of LDL and high-density lipoprotein. The environmental influences that can be controlled are tobacco smoking and diet. What remains then for an implementation policy is to determine how and when we can identify those at risk and what measures should be employed.

For adults, a population strategy seems appropriate beyond measures for the individual because such a strategy clearly will (at least for susceptible populations) reduce the incidence of premature coronary heart disease. A population strategy means a recommendation of a diet for the whole population. Surprisingly, thus far in a high-risk population such an approach has not regularly reduced *mortality* in all of the groups having the intervention, although the incidence of coronary heart disease decreased significantly.

Children are another matter. They need energy and a variety of nutrients at higher levels to promote optimal growth. The "prudent diet" containing 30% of energy as fat and no more than 10% of energy as saturated fat can be adequate for most, and possibly all, children if (1) attention is paid to the composition of the diet to ensure adequate amounts of iron, zinc and other micronutrients; and (2) the diet is, in fact, eaten! Some children will not readily spend the time to consume all of the needed calories when given foods of low energy density.

When should screening begin and whom should be screened? There is no ideal answer to this question at present, so that we may make individual choices with rationale and impunity. Those who say that public policy cannot await solid scientific proof are correct when there is imminent danger. Such danger hardly seems to be present when the pathologic process involved follows childhood and is reversible in adolescence and young adult life.

Screening children only from high-risk families will miss a substantial number of those with moderately high LDL levels. On the other hand, since there are genetic factors involved, finding a high LDL level in a child from an affected family almost surely identifies a child at greater risk than one whose high levels are discovered by a random determination.

The children in the study by Lifshitz and Moses[1] were from high-risk families, so that their identification seems sensible. Having them eat a prudent diet, while not of proven benefit or importance, also seems sensible. The error in 20% (8/40) of these cases was in the failure to monitor the children's growth and intake of all necessary nutrients. Pediatricians are well advised to use the services of nutritionists when advising strict dietary compliance. They should take for themselves the responsibility of carefully monitoring growth and pubertal development in these circumstances.

LAURENCE FINBERG, MD
State University of New York
Health Science Center at Brooklyn
450 Clarkson Ave, Box 49
Brooklyn, NY 11203

1. Lifshitz F, Moses M. Growth failure: a complication of dietary treatment of hypercholesterolemia. *AJDC*. 1989;143:537-542.

The Current State of Pertussis and Pertussis Vaccines

A Report on the Fifth International Symposium on Pertussis

More than 180 participants from 51 countries convened in September 1988 in Copenhagen, Denmark, to review the current status of pertussis and pertussis vaccines. The conference was hosted by Tokai University of Japan, which operates an educational center in Denmark. Professor Mikio Kimura, in concert with Asst Prof Harumi Kuno Sakai, President Tatsuro Matusmae, and Dean Shogo Sasaki, all from Tokai University, together with Charles Manclark, chief of the Laboratory for Pertussis, Food and Drug Administration, James Cherry, professor of pediatrics at UCLA, and Edward Mortimer, professor of epidemiology and biostatistics, Case Western Reserve University, Cleveland, Ohio, constituted the program committee for this Fifth International Symposium on Pertussis.

The conference heard a variety of speakers detail the current status of pertussis in the developed and developing world. In some parts of the world, one child under 5 years of age dies of pertussis every 52 seconds! In contrast, effective immunization procedures have decreased the frequency of disease in the developed world to a few thousand cases a year. The participants also were reminded of the increase in pertussis cases in the United Kingdom and in Japan, following decrease in use of the vaccine. It was also noted that West Germany has experienced considerable disease since the vaccine is not routinely recommended and some parts of West Germany have vaccine uptakes as low as 7%.

In the United States, Hutchins and colleagues from the Centers for Disease Control, Atlanta, Ga, reported that during the period from 1982 to 1986, a total of 14 418 cases of pertussis were reported by two systems used by the Centers for Disease Control. The annual incidence rose from 0.82 per 100 000 in 1982 to 1.74 per 100 000 in 1986. Infants less than 6 months of age had the highest average annual incidence, estimated at 55 cases per 100 000 during the interval. Relative increases were noted for individuals in the adolescent and above 20 years old age groups; in 1985, 12% of reported cases were in these groups in contrast to only 5% in 1982.

Pertussis in adults has increased, and Dr Hewlett from the University of Virginia, Charlottesville, reported several instances of outbreaks, and cited previously reported occurrences of pertussis among adults. He offered the interesting proposition that we consider routine booster doses of pertussis vaccine, possibly every 10 years, along with the adult tetanus-diphtheria boosters. He also pointed out the difficulties in establishment of such a policy, given both lay and medical resistance to adult immunization with pertussis vaccines.

The remainder of the conference was devoted to consideration of issues concerning the current whole-cell vaccine and the use of acellular vaccines, largely developed in Japan. In addition, future prospects for modern molecular biologic approaches to vaccine development were presented.

In 1974 and 1975, two children died within 24 hours of receipt of pertussis vaccine (as the combined diptheria, tetanus toxoids, and pertussis vaccine) in Japan. As a result, vaccine uptake decreased, and in subsequent years, a rise in the incidence of pertussis, associated with a sharp increase in deaths from the disease, was noted. In 1981, Japan introduced acellular pertussis vaccine, as an alternate to whole-cell vaccine; initially it was given to children 2 years of age or older. A number of Japanese investigators reported on the use of this vaccine in various parts of Japan, which now total more than 50 million doses administered.

One complicating factor that was noted by many speakers and discussants is the fact that a variety of manufacturers produced the vaccine, and that their products differed somewhat from each other. General conclusions from these various studies are as follows: (1) the vaccine appears to be less reactogenic than whole-cell vaccine, in terms of local reactions and some systemic reactions, such as fever, irritability, and drowsiness; (2) the vaccine appears to be protective, based on comparison of pertussis occurring in vaccinees intimately exposed to disease and to nonvaccinees in the same circumstances; (3) a few children developed edema locally, and of the entire limb in which the vaccine had been administered; and (4) current studies indicate that infants given the acellular vaccine react with antibody production and that protection appears to be afforded.

Dr Mortimer reported on a careful household contact study in Japan, using one of the acellular vaccine formulations. In this study, efficacy by repeated analyses approximated 81% to 98% protection for household contacts.

In the United States, acellular vaccine has been tested in various sites. One product, produced by Takeda Chemicals Industries Ltd, Japan, has been combined with diphtheria and tetanus toxoids by Lederle Laboratories, Wayne, NJ, and tested by a consortium of investigators. Local reactions appear to be less frequent than with whole-cell vaccines and antibody production to the principal antigens in the vaccines appears to be stimulated in 4- to 6-year-old children, and in 17- to 24-month-old-children. Ongoing studies in younger infants are under way and include both a short-term open study and a longer-term study. Results thus far suggest less fever, less persistent crying, and less unusual cry among infants receiv-

ing the acellular-containing DTP, when contrasted to whole-vaccine–containing DTP. Among infants receiving 5000 to 6000 doses of vaccine, one hyporeactive-hyporesponsive (collapse) syndrome occurred and three seizures were noted.

Dr Cherry's group at UCLA reported preliminary results of an ongoing surveillance study of persistent crying and hypotonic-hyporesponsive episodes following routine DTP immunization. Significantly higher white blood cell counts and lymphocyte counts were noted in children who had these reactions when contrasted to nonreactors. Plasma insulin and glucose levels were not different. Localized inflammation of significant degree was noted in children with persistent crying, suggesting that the inflammatory response may be a cause of this reaction.

Many other clinical aspects of pertussis immunization were presented. One interesting contrast was differing attitudes toward the validity of a pertussis vaccine encephalopathy. Dr John Stephenson from Glasgow, Scotland, presented a closely reasoned argument, based on analysis of all previous reports and a detailed look at the British National Childhood Encephalopathy Study, which suggested that there is no evidence that pertussis vaccine produces encephalopathy. In contrast, Dr David Miller, a major architect of the British encephalopathy study, argued that even with stringent definitions and analysis of the study, there remained a residual number of children for whom no explanation remained for the encephalopathy other than association with pertussis vaccine. Both of these viewpoints have recently captured national attention in the landmark judicial opinion in the so-called Loveday case, argued before a high court in Great Britain. In this opinion, the chief justice of the court indicated that there was no convincing evidence for a pertussis vaccine encephalopathy.

The conference concluded with a look into the future. Paul Fine from the London School of Hygiene and Tropical Medicine suggested that global eradication of pertussis may be an illusory objective. The strategy of surveillance, containment, and contact-tracing, so successful in smallpox eradication, would prove very difficult to impossible for pertussis, given the difficulties in diagnosis and the high attack rate among exposed susceptibles.

A series of investigators examined the various components of *Bordetella pertussis* in an attempt to delineate the toxic and immunologic properties of these antigens, and their functional pathophysiologic effects. Finally, genetic engineering possibilities were invoked by some investigators as a possible future strategy to produce effective immunizing materials.

The conference brought together some of the best minds in the world who are dealing with pertussis and pertussis vaccines of various types. A simple conclusion is not possible, given the gaps in our knowledge, the enormous epidemiologic difficulties in conducting effective and valid studies, and the controversial interpretations of much of the data generated for whole-cell vaccine adverse events and for efficacy of the acellular products. Useful exchanges occurred during the discussions, and more importantly in the planned and impromptu meetings during the symposium; these exchanges will result in further studies with the objective of providing us with an effective vaccine(s), and a strategy for testing it, and for developing a safer, equally effective (or better) alternative to our current use of whole-cell vaccine.

Not to be lost in all the scientific inquiry and debate is the fact that the whole-cell vaccine is effective, has minimal to absent risks for serious sequelae, but can be improved on by development of a vaccine which is equally effective, but with less local reactogenicity. This viewpoint argues for us to continue to use pertussis vaccine as currently advised in the United States, as well as to continue to test the acellular products in a systematic, valid way to determine whether this is the approach that should be substituted for our current strategy. It is hoped that those technical wizards laboring in laboratories throughout the world may identify a better antigen(s) and a better way to produce it so that we can move forward in prevention of a disease that is estimated to kill 606 000 children less than 5 years of age in the world annually.

As a local underscore to the importance of these activities, at the time of this writing, Arizona has experienced an epidemic of pertussis that has involved more than 260 children and adults, with at least one death attributed to this disease. As might be anticipated, many of these individuals were unprotected by vaccine. As a discipline, we must be diligent in applying the current vaccine to the population at risk and to educate the public and younger physicians alike to the benefits of vaccine and to the safety of the products we now use. Public perception, guided by a few physicians who misinterpret the data, suggests that whole-cell vaccine is "dangerous" and should be avoided at all costs. This erroneous perception allows for local outbreaks of a disease that is far more "dangerous" than even the most exaggerated estimates of vaccine effects. Pertussis is a potentially lethal disease; the vaccine is effective and safe, even if it has some undesirable local and systemic effects, the huge majority of which are transient and without danger to life or limb. We must convince ourselves and our public that this is the case, and we must use pertussis vaccine to prevent this terrible disease.

VINCENT A. FULGINITI, MD
Editor, *AJDC*
Dean's Office, Room 1529
Tulane University School of Medicine
1430 Tulane Ave
New Orleans, LA 70112

Quotables

Preconceptions: *Our preconceptions are so powerful that when we find data that contradict them, we tend to rationalize the data as exceptions, or to misinterpret them in other ways.*

BENSON E. GINSBURG

The Editorial Board Speaks . . .

Albert W. Pruitt, MD

In an earlier brief biography (*AJDC*. 1986;140:749) we indicated that Al was simultaneously interim dean, chairman of the department of pediatrics, and E. C. Hawes professor of pediatrics at the Medical College of Georgia, Augusta. He has just given up the responsibilities of interim dean but remains as active as ever in his other professional pursuits. He was recently appointed as consultant to the Office of Substance Abuse Prevention, Washington, DC, has received a variety of research grants to pursue pharmacologic research, and continues to receive honors and to participate in local community, regional, and national professional activities. For example, he was appointed to the Commission on Ministry of the Episcopal Diocese of Georgia, was a visiting professor at Bowman Gray School of Medicine, Winston-Salem, NC, and is active in the American Academy of Pediatrics, the American Medical School Pediatric Department Chairmen's Group, and various other societies. Most recently he has become a DeLand Fellow in Health Care and Society at the Brigham and Women's Hospital in Boston, Mass. He continues to publish articles on calcium channel blockers in the treatment of children and writes informative sections for textbooks, such as the chapter on systemic hypertension in the *Nelson Textbook of Pediatrics* (Philadelphia, Pa: WB Saunders Co; 1987:1027-1031). His essay below recognizes unsung contributors to our education, our careers, and our sense of "being." His thoughts remind all of us of our indebtedness to these persons in our past who usually remain unrecognized.

THANK YOU ROBIN AND RICHARD

Many of us, now 20 years or so out of residency, are at about the midpoint of the most active phase of our careers as pediatricians. Recognition of that fact prompts reflection—reflection about what set us on our course, reflection about the springs from which our lives as professionals have flowed. Such reflection can only prompt in us a profound sense of gratitude, and, of course, all real gratefulness calls us to examine our own giving.

We owe most obvious debts to our patients and to our teachers. Especially during those early years of learning, patients gave us a gift that must be reverenced. Perhaps the term *patients* was particularly merited by those with whom we began. We all remember the gentleman who, three times a week, would kindly give his medical history to a small group of awestruck sophomore students, and then allow them, one by one, to palpate his abdomen. There were dozens of these *patients*—patient with us and hopeful, not only that they might be helped by our inquisitiveness but, indeed, that we might also be helped. Without the willingness and participation of those people, we never would have begun to develop the skills that we now so freely use in the treatment of a second, third, or fourth generation of patients. We cannot know whether those people, way back there, were ever conscious of the gift they gave us. Mostly, they thanked us, but we really should not forget to thank them in whatever ways we can.

As pediatricians, we have been given gifts by another group of people, for it has been necessary for us to ask parents to share with us, to share something more precious even than their own health care, that is, the health care of their children. It is one thing to put up with awkwardness and inexperience for oneself. It is quite something else to put up with such things in a person who is treating your child. Do we not, most of us, know this acutely from our own experience? However, while we were at our most awkward, our most inexperienced, we asked parents to entrust the health of their children to us; we asked them to allow their children to become a part of our development. What did we offer in return? We had some knowledge by then, of course, but mostly we offered availability, openness, loyalty, and dedication to them and to their children and to the health of future generations of children. We would get better; we believed that and worked for it. Perhaps these parents believed that too. I hope so, and I hope that some, at least, knew that they were giving to us and to other children when they thanked us for the care we had provided for their own children. We probably did not know enough to thank them then. At the time it seemed a necessary and, for the most part, even trade, but gifts are not even, and never can be. That is why gifts cannot be repaid, as debts can.

We all are indebted also. During those years of supervised learning and training we had teachers—teachers who sometimes seemed larger than life, teachers who knew so much more than we did that they seemed to belong to a different order of magnitude. They pushed us, pulled us, chided us, berated us, and begged us, in effect, to become as good as they were. At the time it never entered our heads that it was their own dedication to the future of the health care of children that dictated their actions.

We stand, at this midpoint in our careers, where our teachers stood 20 years ago. As those teachers retire one by one, we are aware of the void their departure apparently creates. Oh yes—we frequently quote from their rounds to our own students. Somehow, these axioms never sound quite as profound when they come from our lips. You had to have been there.

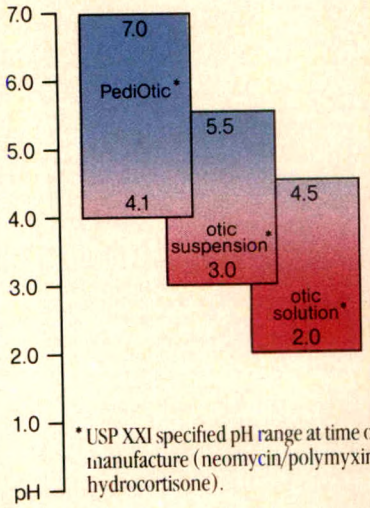
Many of these teachers took on the responsibility for establishing and supporting outstanding programs that would provide access to compassionate health care for increasing numbers of families and children. Although these teachers were often as poorly compensated as their students, their loyalty to student and patient needs never reflected this. They were devoted to both, and they were devoted to our growth and to the future of health care for the children of this country. Their generous gifts have made us richer. In return, they wanted us curious and they wanted us responsible and they wanted us committed to that same future. That is our debt. We cannot, of course, repay them, any more than we can repay those patients and parents.

Our time has come. We are called on now for the critical review, the wise counsel, and the unending availability that were offered to us. We are called on to be, if not larger than life, at least as large of spirit and as generous as those who have shared what they had with us. The gifts that were put in our hands we must now give in full measure. To do anything less is to deny the value of what we ourselves were given.

PediOtic® suspension sterile

Formulated to be less acidic to help minimize irritation.

A more normal pH range means less potential for painful irritation.



*USP XXI specified pH range at time of manufacture (neomycin/polymyxin B/hydrocortisone).

Formulated to help take the sting out of otitis externa therapy

PediOtic suspension is specially formulated to have a higher pH range than conventional otics.

Children may be less likely to resist its instillation, and their parents will appreciate the ease of compliance.

And you can prescribe PediOtic suspension with confidence, knowing it contains the same proven antibiotic/anti-inflammatory combination physicians have trusted for years.

Now there's a gentle effective treatment for "swimmer's ear" to please patient, parent, *and* physician.

Please see brief summary of prescribing information on next page.

PediOtic® suspension sterile

Wellcome

(polymyxin B sulfate-neomycin sulfate-hydrocortisone)

PediOtic® suspension sterile

(polymyxin B sulfate-neomycin sulfate-hydrocortisone)

DESCRIPTION: Pediotic suspension (polymyxin B sulfate-neomycin sulfate-hydrocortisone) is a sterile antibacterial and anti-inflammatory suspension for otic use. Each ml contains: Aerosporin® (polymyxin B sulfate) 10,000 units, neomycin sulfate equivalent to 3.5 mg neomycin base, and hydrocortisone 10 mg (1%). The vehicle contains thimerosal 0.001% (added as a preservative) and the inactive ingredients cetyl alcohol, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, propylene glycol, and Water for Injection. Sulfuric acid may be added to adjust pH. Pediotic suspension has a minimum pH of 4.1, which is less acidic than the minimum pH of 3.0 for Cortisporin® Otic Suspension.

INDICATIONS AND USAGE: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia, and varicella infections.

WARNINGS: This product should be used with care in cases of perforated eardrum and in longstanding cases of chronic otitis media because of the possibility of ototoxicity. Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known. When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS: Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported (see WARNINGS section). Adverse reactions have occurred with topical use of antibiotic combinations including neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in two of 2,175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]

The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. Stinging and burning have been reported rarely when this drug gained access to the middle ear.

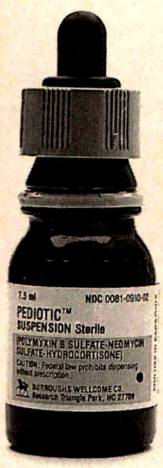
HOW SUPPLIED: Bottle of 7.5 ml with sterilized dropper. NDC 0081-0910-02. Store at 15° to 25°C (59° to 77°F).

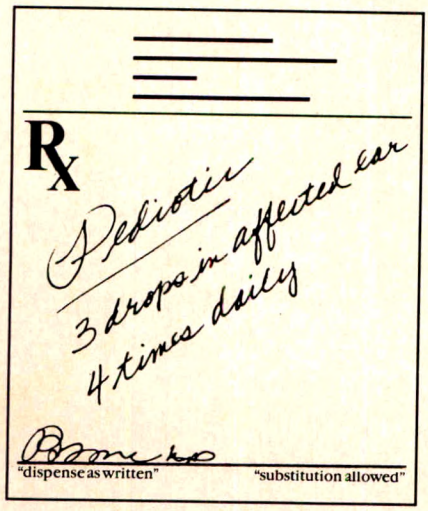
REFERENCES: 1. Leyden JJ, Kligman AM: Contact dermatitis to neomycin sulfate. *JAMA* 1979;242:1276-1278. 2. Prystowsky SD, Allen AM, Smith RW, et al: Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. *Arch Dermatol* 1979;115:959-962.

BURROUGHS WELLCOME CO., Research Triangle Park, NC 27709

Copr. © 1989 Burroughs Wellcome Co. All rights reserved.

PED-101R





Formulated to help take the sting out of otitis externa therapy.

BC/BE Pediatrician Wanted

to join three member pediatric group in Aurora, Illinois.

If interested, please call Mrs. Cooke, Office Manager, for information, appointment and interview. Area Code (312) 896-7788

Washington

Wenatchee Valley Clinic, a multispecialty group in North Central Washington, is currently recruiting for a BC/BE pediatrician to join one pediatrician in a busy general practice. Excellent facilities at both clinic and hospital. Excellent salary and benefits. Prime outdoor recreational area.

Contact:

Terry Coplin
840 Hill Avenue
Moses Lake, WA 98837
(509) 765-0216

Growth Failure

A Complication of Dietary Treatment of Hypercholesterolemia

Fima Lifshitz, MD, Nancy Moses, MNS, RD

• **We describe 8 children among a group of 40 in whom growth failure was associated with unsupervised dietary treatment of hypercholesterolemia. In 3 children, nutritional dwarfing ensued, and in 5, weight loss or insufficient weight gain occurred. Children with growth failure consumed significantly less energy and zinc than those children growing well. The dietary intakes of the 3 children with nutritional dwarfing were the most markedly deficient in total energy, fat, and micronutrients. These data suggest that the diagnosis and dietary treatment of hypercholesterolemia have potentially adverse consequences. Overzealous application of a low-fat, low-cholesterol diet may lead to growth failure due to inadequate intake of energy, vitamins, and minerals. Careful monitoring of children receiving modified fat and cholesterol intakes for hypercholesterolemia treatment is mandatory to ensure adequate nutrition for normal growth and development.**

(*AJDC*. 1989;143:537-542)

It has been reported that the US adult population consumes approximately 37% of total energy in the form of dietary fat, about three times more saturated fatty acids than polyunsaturated fatty acids, and an average daily cholesterol intake of 0.69 mmol (266 mg) for women and 1.05 mmol (405 mg) for men.[1] To lower the risk of coronary heart disease (CHD), recommendations have been made to all Americans to reduce their intake of total dietary fat and cholesterol.[2-5] The American Heart Association[3] advocates that the general public consume a "prudent" diet containing 30% of energy as fat with less saturated fat, more monounsaturated and polyunsaturated fatty acids, and no more than 0.78 mmol (300 mg) of cholesterol per day.[3]

For editorial comment see p 531.

Accepted for publication December 19, 1988.

From the Department of Pediatrics, North Shore University Hospital, Manhasset, NY (Dr Lifshitz and Ms Moses), and Department of Pediatrics, Cornell University Medical College, New York, NY (Dr Lifshitz).

Reprint requests to Department of Pediatrics, North Shore University Hospital, 300 Community Dr, Manhasset, NY 11030 (Dr Lifshitz).

In contrast, other groups, such as the Food and Nutrition Board,[6] the National Research Council,[7] the American Council on Science and Health,[8] the American Academy of Pediatrics,[9] and numerous independent researchers,[10-12] believe that there is no justification for recommending that all healthy Americans reduce their intake of fat and cholesterol. However, for patients with hyperlipidemia or proved vascular disease, individualized diet modification is viewed as an important component of overall management.[9,10,13]

Few studies have evaluated the benefits and the risks of dietary recommendations given to children with hypercholesterolemia.[9] We describe 8 patients with growth failure among a group of 40 children who were advised by their pediatricians to eat a low-fat, low-cholesterol diet for the treatment of hypercholesterolemia. The patients with growth failure had families with clusters of risk factors for CHD, particularly traumatic events like heart surgery and heart attacks. They consumed inappropriate diets with insufficient energy and micronutrients to sustain normal growth and weight gain.

PATIENTS AND METHODS

Forty children were referred in 1986-1987 to the Nutrition Center, Division of Pediatric Endocrinology, Metabolism and Nutrition, Department of Pediatrics, North Shore University Hospital, Manhasset, NY, because of hypercholesterolemia. The pertinent characteristics of these children are shown in Table 1. All patients had an elevated serum cholesterol level identified by their pediatricians on routine screening. The cholesterol screening was made at the request of the family in only one of the patients. The children had no medical abnormalities other than hypercholesterolemia. Following the diagnosis of hypercholesterolemia in each patient, general advice was given by the referring physician to reduce the levels of fat and cholesterol in the patient's diet. The advice and specific dietary recommendations varied in each case and therefore could not be assessed. However, the manner in which the patient and family presumably applied the information and advice given by the referring pediatrician was evaluated by the analysis of the patient's dietary intake and food patterns at the time of evaluation at our Nutrition Center.

The children were seen at the Nutrition Center 2 weeks to 4.5 years after the diagnosis and after dietary recommendations for hypercholesterolemia were first made by the patients' physicians. In all patients, a growth record was obtained from the family and/or from the patient's physician. Weight and height records throughout life were analyzed by plotting them on standard growth charts.[14] Ideal body weight for height at the 50th percentile was determined from the National Center for Health Statistics growth percentile charts.[14] For assessment of body composition, arm muscle area and arm fat area were calculated from midarm cicumference and tricep skinfold thickness measurements as described by Frisancho.[15] All but the five oldest patients were Tanner stage I; four of them were stage II and one was stage III.

At the initial evaluation at the Nutrition Center, the patients were divided into groups in accordance with their growth pattern and body weight progression after diagnosis and/or treatment of hypercholesterolemia. Thirty-two patients were considered to have *normal growth*. Their height and weight were progressing along the same percentile throughout life. In these children, there were no deviations in growth patterns after diagnosis of hypercholesterolemia and unsupervised dietary treatment. Eight patients were considered to have *growth failure* associated with the dietary treatment of hypercholesterolemia. In three of these eight patients, the growth pattern following diagnosis and treatment of hypercholesterolemia was similar to the nutritional dwarfing pattern according to anthropometric indexes of the Welcome Trust Classification.[16] In the other five patients, a drop in body weight without linear growth alterations was noted; their weight fell across at least one major percentile line after diagnosis and unsupervised dietary treatment of hypercholesterolemia.

At the Nutrition Center, a nutritional assessment was performed to evaluate the dietary intake of each patient since diagnosis of

Table 1.—Characteristics of Children With Hypercholesterolemia in Accordance With Their Growth Patterns*

	Normal Growth	Growth Failure
Sample size, No. M/F	12/20	5/3
Age at diagnosis, y†	7 1/12 ± 2 7/12	10 1/12 ± 3 3/3‡
% IBW†	110.6 ± 19.6	91.4 ± 8.3§
Serum cholesterol, mmol/L (mg/dL)†	6.26 ± 1.22 (241.9 ± 47.2) (n = 32)	6.21 ± 1.12 (240.2 ± 43.5) (n = 8)
High risk, No.‖	32	8
Moderate risk, No.¶	0	0
Serum triglycerides, mmol/L (mg/dL)†	1.18 ± 0.49 (104.7 ± 43.7) (n = 27)	0.89 ± 0.21 (78.9 ± 18.2)‡ (n = 6)
High risk, No.‖	12	2
Moderate risk, No.¶	15	4
Serum LDL, mmol/L (mg/dL)†	4.24 ± 1.51 (164.1 ± 58.2) (n = 22)	4.31 ± 5.3 (166.8 ± 20.5) (n = 3)
High risk, No.‖	18	3
Moderate risk, No.¶	2	0
Serum HDL, mmol/L (mg/dL)†	1.24 ± 4.34 (48.0 ± 16.8) (n = 27)	1.27 ± 2.25 (49.2 ± 8.7) (n = 4)
High risk, No.#	6	0

*IBW indicates ideal body weight; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
†Data are means ± SDs.
‡$P<.05$ compared with the normal growth group.
§$P<.03$ compared with the normal growth group.
‖Number of patients with values at or above 90th percentile of standard.[19]
¶Number of patients with values between 75th and 90th percentile of standard.
#Number of patients with values at or below fifth percentile of standard.

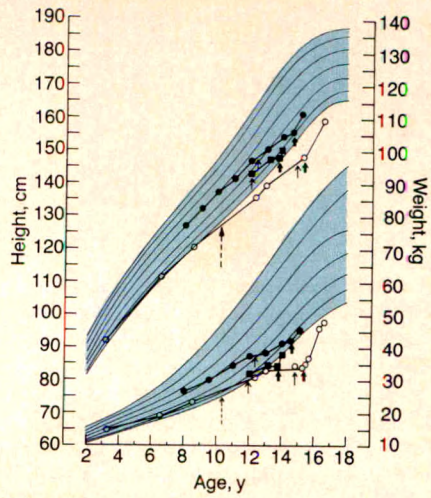


Fig 1.—Growth data for three children with growth failure. The extreme growth percentiles shown denote the fifth and 95th percentiles. The diagnosis of hypercholesterolemia and initiation of dietary treatment by the pediatrician are indicated by a thin arrow. In the patient represented by open circles, the dashed arrow represents onset of father's heart problems and dietary restrictions. The thick arrow denotes intervention with appropriate nutritional counseling.

hypercholesterolemia. This evaluation included a detailed 24-hour dietary recall, as well as an assessment of the eating patterns and food preferences of the patient.[17] Dietary analyses were performed by a microcomputer-based nutrient analysis system (Nutriquest II, Kensington, Md).[18] All patients were subsequently given detailed dietary advice and nutritional counseling by a nutritionist for treatment of hypercholesterolemia. The nutritionist conducted structured training sessions with the family, usually the mother, and with the patient on selection of a well-balanced diet within the following guidelines. The patients and their families were instructed to adjust total fat intake to 30% of the energy and cholesterol intake to 0.26 mmol (100 mg) per 4200 J (1000 calories), not to exceed 0.65 to 0.78 mmol (250 to 300 mg) of cholesterol per day. Saturated fat intake was recommended to be no more than 10% of total energy, and a ratio of polyunsaturated to monounsaturated to saturated fatty acids of 1:1:1 was to be achieved. Emphasis was placed on consuming sufficient energy to support normal growth and development.

The serum lipid levels of the patients at diagnosis of hypercholesterolemia were placed in high or moderate risk percentile categories.[19] For serum cholesterol, triglyceride, and low-density lipoprotein cholesterol levels, high risk was defined by values greater than or equal to the 90th percentile for age and sex. The moderate risk category had values greater than or equal to the 75th percentile but less than the 90th percentile for age and sex. For high-density lipoprotein cholesterol levels, high risk was defined as values less than or equal to the fifth percentile for age and sex. Laboratory measurements of the serum lipid levels were performed at different clinical laboratories by standard techniques after an overnight fast. Thus, owing to interlaboratory variability, the data on individual patients could not be compared to assess the response of serum cholesterol level to dietary treatment recommended by the referring pediatrician. The biochemical change in serum cholesterol levels was only reported in the patients who were closely followed up in our center and who had serial serum lipid measurements done by the same laboratory. Only 18 of the 40 patients agreed to return to the Nutrition Center for long-term follow-up and treatment of hypercholesterolemia. The others returned to the referring physician for continuing care.

The presence and severity of risk factors for CHD were evaluated as follows. Each of the following items found in the family history of parents and/or siblings was given the numerical value shown: heart surgery (coronary bypass), 4; heart attack, 4; angina, 2; hypertension, 2; obesity, 2; diabetes mellitus, 2; and a history of diet modification by the family to reduce the risk of CHD, 2. Each of these risk factors occurring before age 50 years was given a twofold value. Risk factors present in grandparents or other relatives were assigned half the score. The serum cholesterol levels in the patients and immediate family members were given the following values: greater than 7.76 mmol/L (300 mg/dL), 4; between 6.21 and 7.76 mmol/L (240 to 300 mg/dL), 3; between 5.69 and 6.21 mmol/L (220 to 240 mg/dL), 2; and less than 5.69 mmol/L (220 mg/dL), 1. Half the score was given to cholesterol levels of the grandparents or other relatives. A total risk factor score was calculated by summing all the values assigned to each of the risk factors in each patient.

Comparisons of data between patients with normal growth and growth failure were made statistically by nonparametric analysis (Mann-Whitney test).

RESULTS

Three of the eight patients in the growth failure group had nutritional dwarfing. They had a falloff in linear growth and cessation of weight gain associated with unsupervised dietary treatment of hypercholesterolemia (Fig 1). One patient showed deteriorating linear growth and cessation of weight gain since age 10 1/6 years following diagnosis of the father's hypercholesterolemia and angina. At that time, the father's dietary intake as well as that of

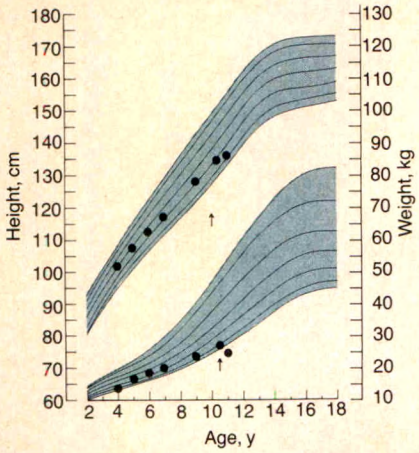


Fig 2.—Growth data of one child with acute weight loss following diagnosis and beginning of treatment of hypercholesterolemia (arrow) of 6.34 mmol/L.

Table 2.—Food Consumption by Children With Hypercholesterolemia in Accordance With Their Growth Patterns*

	Normal Growth	Growth Failure
Milk, mL		
Skim	334.5±298.6 (7)	240 (1)
99%	190.6±81.0 (11)	300, 360 (2)
98%	218.4±165.5 (6)	180 (1)
Whole	240.0±216.3 (3)	0
Dairy products	1.5±0.5 (12)	0.5 (1)
Red meat	3.3±2.0 (13)	2.3±0.6 (3)
Eggs	0.7±0.7 (5)	0
Poultry	3.1±1.1 (18)	3.0±1.0 (3)
Fish	2.8±0.9 (7)	0
Pastries	2.7±1.6 (21)	1.6±0.5 (5)
Candy	1.2±0.4 (11)	1 (1)
Frozen milk desserts	1.2±0.5 (10)	1 (2)

*Data are derived from a 24-hour dietary recall and are means±SDs. Numbers in parentheses indicate numbers of patients ingesting each item. All entries except those for milk indicate numbers of servings, determined as follows: for dairy products and eggs, serving sizes were based on American Diabetic Exchange Lists[19]; for pastry, one serving equals one cookie or one piece of cake or pie; for candy, one serving equals one piece; and for frozen milk desserts, one serving equals one half cup.

the entire family was modified to reduce fat and cholesterol. Subsequently, the father had coronary bypass surgery, and the patient at age 14¾ years was also found to have hypercholesterolemia. The identification of elevated serum cholesterol levels in the patient led to further dietary restrictions of fat and cholesterol with continued deterioration of the patient's growth and lack of progression of puberty (Tanner stage II). The other two patients also had deteriorating weight and linear growth with no appearance of secondary sexual characteristics (Tanner stage I) after diagnosis of hypercholesterolemia and unsupervised dietary treatment. After the initial assessment and nutritional counseling by a nutritionist in the Nutrition Center, these patients gained weight at a rate of 4 to 7 kg/y and grew at a rate of 6.0 to 7.6 cm/y, while their serum cholesterol levels decreased 10% to 28%.

The remaining five of the eight patients in the growth failure group lost weight or failed to gain weight following diagnosis and unsupervised dietary treatment of hypercholesterolemia. A representative example of the growth data of a patient with weight loss is shown in Fig 2. Three of these five patients were given long-term nutritional counseling by a nutritionist in the Nutrition Center and weight gain resumed while normal growth continued. Concomitantly, the reduction in the serum cholesterol levels of these three patients was 0%, 17%, and 27% while ingesting a diet that provided adequate energy for growth with 30% of the energy from fat and 0.65 to 0.78 mmol (250 to 300 mg) of cholesterol per day. The other two patients did not return for follow-up evaluation or have serum cholesterol levels reevaluated.

Children with growth failure were underweight for height (Table 1). The body weight deficit for height was particularly noticeable in the five patients who had body weight alterations. Only two of the three children who had nutritional dwarfing had mild body weight deficits of 8% and 11%. The majority of the patients with normal growth had appropriate body weight for height, both progressing between the fifth and 95th percentiles. Thirteen patients in the normal growth group were overweight (11% to 53% excess weight for height). The arm muscle areas of children with growth failure and normal growth fell within the normal range (fifth to 95th percentiles), except for one child in each group in whom the arm muscle area was below the fifth percentile. Arm fat area was not depleted (below the fifth percentile) in any patient; levels above the 95th percentile were reported in nine patients in the normal growth group (five overweight children and four children with appropriate weight for height).

All patients had hypercholesterolemia as defined by serum cholesterol levels above the 90th percentile for age and sex (Table 1). The serum low-density lipoprotein levels were also generally increased. There were no differences in serum cholesterol or low-density lipoprotein levels among the patients with or without growth abnormalities. However, the serum triglyceride concentrations were lower in the patients with growth failure ($P<.05$).

The patients with growth failure were generally older than the patients with normal growth (Table 1) and the three oldest patients were those with nutritional dwarfing (Fig 1). Also, patients with growth failure had a longer delay in referral to the Nutrition Center for nutritional counseling than patients without growth alterations. The mean duration from the time of diagnosis and unsupervised dietary treatment of hypercholesterolemia before nutritional consultation was sought was 20.1±0.9 months (mean±SD) for the patients with growth failure, compared with 3.9±2.8 months for those without growth alterations ($P<.001$).

The contribution of the individual and familial risk factors associated with CHD to the manner in which the patient and family applied the advice given by the referring pediatrician for the dietary treatment of hypercholesterolemia was also different among the two groups of patients. Those with growth failure had a higher mean total score of risk factors for CHD than those with normal growth (mean±SD, 12.6±6.2

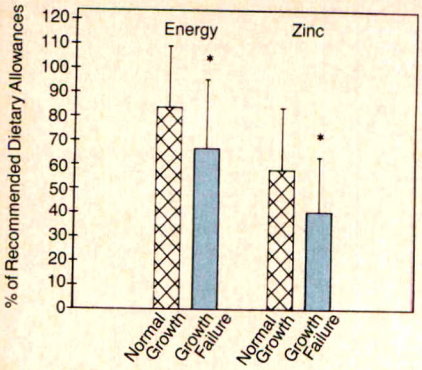


Fig 3.—The percent of energy requirements for ideal body weight for height, age, sex, and zinc intake expressed as a percent of the recommended dietary allowances are shown for each group (mean ± SD). Data were obtained from a 24-hour dietary recall of the food ingested by the patients prior to nutritional counseling at the Nutrition Center. Numbers of children in each group were the same as in Table 1. Asterisks indicate $P<.05$ by Mann-Whitney test as compared with the normal growth group.

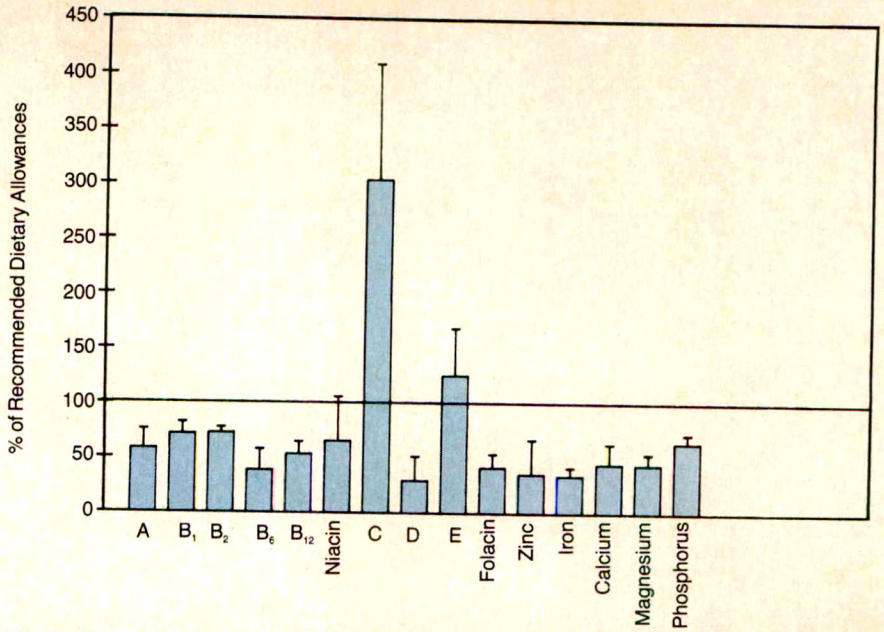


Fig 4.—The vitamin and mineral intakes of three children with hypercholesterolemia who demonstrated nutritional dwarfing are reported as percents of the recommended dietary allowances for age and sex. These patients consumed less than 60% of the recommended energy for age and sex, and the proportion of energy derived from dietary fat was only 20.5% ± 2.1%. Data were obtained from a 24-hour dietary recall of the food ingested by the patient before nutritional counseling. Data are expressed as mean ± SD.

vs 8.4 ± 4.3, respectively; $P<.05$). Patients with growth failure were from families who had experienced acute problems, particularly heart surgery and heart attack occurring at a young age, and who were dieting to reduce high serum cholesterol levels. However, some of the CHD risk factors also occurred in isolation in patients without growth abnormalities, although in these patients, several risk factors were not clustered together in the same family.

Food consumed by children after the diagnosis of hypercholesterolemia and the referring physician's dietary recommendations to lower fat and cholesterol intake in accordance with the growth pattern is shown in Table 2. In general, all the patients were advised to reduce their intake of dairy products, specifically whole milk and butter, red meat, shellfish, and eggs to reduce dietary fat and cholesterol. This dietary advice did not appear to differ among the two groups of patients. However, the type of food consumed by the patients with growth failure differed from that consumed by patients with normal growth. Some patients in the latter group continued to ingest whole milk and eggs, whereas the children with growth failure did not.

Also, there were quantitative changes in the nutrient intake among the two groups of patients. The total energy and zinc contents of the diets of patients with growth failure were significantly less than those of patients with normal growth (Fig 3). The food consumed by the patients with growth failure provided an average of 66% of the energy requirements and 40% of the daily zinc requirements for their ideal body weight, age, and sex. In contrast, the patients with normal growth were reported to consume an average of 84% of the energy requirements and 58% of the daily zinc requirements ($P<.05$).

The dietary intake of all patients was low in fat and cholesterol following the diagnosis of hypercholesterolemia and referring physicians' dietary recommendations. Patients with normal growth ingested an average of 29.6% ± 8.1% of energy derived from fat; patients with growth failure consumed a similar percentage of energy derived from fat (25.4% ± 2.9%; $P>.05$). The total cholesterol intake of both patients with normal growth and those with growth failure was also similar (0.35 ± 0.17 mmol/d [133.7 ± 63.0 mg/d] vs 0.27 ± 0.20 mmol/d [106.1 ± 78.7 mg/d], respectively; $P>.05$). The amount of protein intake was appropriate in all instances and no differences were noted among the two groups of patients. The mean percent of energy derived from protein was 14.6% and 15.9% in the growth failure and normal growth groups, respectively, with an average intake greater than 2 g/kg per day for both groups of patients. Similarly, there were no statistical differences in the intakes of the other micronutrients among the patients with normal growth and those with growth failure. However, the mineral intakes of most patients were lower than the recommended dietary requirements for age and sex.

The dietary intake of the three patients with nutritional dwarfing was the most markedly deficient. These patients consumed the smallest percentage (<60%) of established energy requirements for ideal body weight, sex, and age, and the proportion of energy from dietary fat was only 20.5% ± 2.1% (mean ± SD). Their diets were also generally inadequate in vitamins and minerals (Fig 4). Intake of vitamins B_6 and D, folacin, zinc, iron, calcium, and magnesium was reported to be less than 50% of the recommended dietary allowance. A decrease to less than 66% of the recommended dietary allowance was noted for vitamins A and B_{12}, niacin, and phosphorus. Only vitamins E and C were consumed in quantities meeting the recommended dietary allowance.

COMMENT

These data demonstrate that the diagnosis and unsupervised dietary treatment of hypercholesterolemia in children may have adverse consequences. A high proportion of patients who were advised to eat a low-fat, low-cholesterol diet because of hypercholesterolemia selected inappropriate diets to sustain normal growth and weight gain and to allow for puberty.

Treatment with a low-fat, low-cholesterol diet for patients with elevated serum cholesterol levels is now the norm.[20,21] Diets for children and adolescents that provide a decreased fat and cholesterol intake and an increased ratio of polyunsaturated to saturated fatty acid may be designed to meet all the recommended dietary allowances.[22] However, in this study, most of the children with hypercholesterolemia consumed low-fat and low-cholesterol diets by reducing their intake of foods such as milk, dairy products, meat, and eggs. These diets often provided insufficient energy and inappropriate quantities of vitamins and essential minerals for growth.[23] Therefore, the possibility exists that even the children with normal growth could have exhibited growth alterations if they had persisted with such limited intake for longer periods without compensating with intake of large quantities of grains and cereals.[24]

The patients who had growth failure in association with the dietary treatment of hypercholesterolemia were generally older, had consumed the most restrictive diets for the most prolonged periods, and came from families who had experienced what appeared to be more traumatic events associated with CHD, including heart surgery and heart attacks at a younger age. These families engaged in dieting to reduce serum cholesterol levels and were not counseled or supervised by a nutritionist for prolonged periods. The contribution of CHD risk factors to the manner in which the patient applied and followed the diet appeared to be cumulative. No single factor, but the combination of all of them occurring simultaneously, was necessary to be associated with growth failure. The older average age of the patients with growth failure suggests that the patients themselves may have had a higher concern and a personal input in exaggerating the dietary restrictions. These were the patients who ate the most profoundly deficient diets. It should be pointed out that there may be some selection bias in the group of patients referred to us, and that it is possible that the high rate of growth failure is not representative of the population at large.

Growth failure and delayed puberty are well-known complications of inappropriate dietary intakes. The low-fat, low-cholesterol diets of the patients with growth failure were mainly inadequate in energy and zinc, two elements that are necessary for normal growth.[25] However, other multiple-nutrient deficits might have played a role in growth failure, since patients with nutritional dwarfing consumed very inappropriate diets. We have recently reported other syndromes in children with growth failure resulting from inadequate nutrition due to other causes such as fear of obesity and inappropriate parental health beliefs.[26-29] It is also known that the consumption of hypocaloric diets for the treatment of childhood and adolescent obesity can produce a reduction in growth rate.[30]

The American Heart Association,[31] the American Health Foundation,[32] the National Institutes of Health Consensus Development Panel,[20] and individual medical authorities[21,33] believe that atherosclerosis has its roots in childhood and that adherence to a prudent diet in early life will lessen the risks of chronic illnesses in later life. However, a reduction in fat intake to less than 30% of total energy may not be routinely warranted in patients with hypercholesterolemia. Such severe dietary restrictions may be warranted under close supervision in those patients who fail to reduce their serum cholesterol levels when following a prudent diet.[20,21]

Physicians' general advice to lower fat and cholesterol intake for dietary treatment of hypercholesterolemia may be insufficient. Children with serum cholesterol levels above the 90th percentile require special dietary instruction and close supervision.[20,21] An extensive nutritional education and surveillance program is needed for the patient and the family to ensure that they are adhering to a well-balanced diet when reductions of dietary fat and cholesterol are prescribed. The physician should keep in mind that some patients and families may either be overzealous in their attempts to reduce serum cholesterol levels through dietary restrictions, or the reverse, they may be noncompliant in following dietary recommendations. The diet needs to be individually designed in accordance with the family's food preferences. Misconceptions regarding the elimination of specific foods, eg, dairy products, red meat, and eggs, need to be dispelled. These foods may be permitted in the diet in an amount sufficient to improve the nutritional quality of the diet without an increase in fat and cholesterol intake above the aforementioned guidelines.

The long-term consequences of diets low in fat, saturated fatty acids, and cholesterol and high in polyunsaturated fatty acids are unknown.[34-37] Questions have been raised regarding the safety of high intakes of polyunsaturated fatty acids, particularly in relation to gallstone formation, cancer incidence, and alterations in cell membrane composition and fluidity. In a number of intervention studies employing fat-modified diets, the decrease in CHD mortality is offset by a corresponding increase in deaths from cancer or other causes such that total mortality in the population remains unchanged.[37] Several epidemiologic studies have shown that low blood cholesterol levels (ie, <4.91 mmol/L [<190 mg/dL]) are associated with an increased incidence of CHD.[9] Although controversial, there is some suggestion that an adequate intake of cholesterol during the entire growth period is important for cholesterol metabolism later in life, for myelination of the nervous system, and for the formation of bile acids and hormones.[38]

IMPLICATIONS

To date, we have the technology to recognize and diagnose hypercholesterolemia with great ease, and pediatricians are availing themselves of cholesterol screening methodology with increased frequency.[39] Virtually everyone accepts an association between cholesterol levels and atherosclerosis and all groups advocate some kind of restriction of saturated fat and cholesterol for the treatment of hypercholesterolemia. Epidemiologic surveys, dietary intervention trials, and studies in experimental animals provide strong evidence

that dietary fat and cholesterol restriction could exert favorable influences on plasma cholesterol levels.[40] There is a problem in the formulation and implementation of diet prescriptions and limitations in educating patients.[41] There is considerable evidence that the majority of individuals do not follow diets on a long-term basis, even when they have a specific need because of disease.[42]

Physicians must be aware of the compounded implications of the diagnosis of hypercholesterolemia and the intricacies of following a low-fat, low-cholesterol diet. Children and families who have had firsthand experience with the devastating consequences of CHD might be overzealous in the dietary restrictions, thereby producing nutritional deficiencies. Physicians must also keep in mind that good habits of exercise, weight control, and smoking avoidance may be as important as monitoring the dietary intake of children with hypercholesterolemia.[9]

SUMMARY

The Committee on Nutrition of the American Academy of Pediatrics recognized the potential problems from eating low-fat, low-cholesterol diets and concluded that any recommendation for a restriction on the dietary patterns during the first two decades of life should be viewed with caution.[9] In this report we have described the potential consequences of not heeding this advice. Growing children, particularly those with a family history of acute heart problems occurring at an early age, who consume a low-fat, low-cholesterol diet may ingest an inappropriate diet to maintain normal growth. This diet could provide insufficient energy and may lack essential nutrients if not adequately supervised. In 20% of the patients described, the diagnosis and treatment of hypercholesterolemia was associated with growth failure due to an inappropriate selection of foods low in fat and low in cholesterol. The patients who exaggerate the nutritional restrictions may be the ones who have lived through the traumatic events of CHD in their immediate families. Pediatricians should be alerted to monitor the diet prescriptions and growth of patients who receive treatment for hypercholesterolemia; a referral of such patients to a registered dietitian with pediatric experience should be recommended.

Dr Lifshitz received a fellowship from the Rockefeller Foundation, Bellagio Study Center, Villa Serbelloni, Bellagio, Italy.

We acknowledge the help in the statistical analysis by Martin Lesser, PhD, Director of Biostatistics at North Shore University Hospital and Cornell University Medical College, New York, NY.

References

1. Carroll MD, Abraham S, Dresser CM. *Dietary Intake Source Data: United States, 1976-80.* Washington, DC: National Center for Health Statistics; 1983. Vital and Health Statistics, series II, No. 231, US Dept of Health and Human Services publication PHS 83-1681.

2. Inter-society Commission for Heart Disease Resources. Special report. *Circulation.* 1984; 70:183A-184A.

3. *Dietary Treatment of Hypercholesterolemia in Adults: A Handbook for Counselors, and a Manual for Patients.* Dallas, Tex: American Heart Association; 1988.

4. US Department of Agriculture and US Department of Health and Human Services. *Nutrition and Your Health: Dietary Guidelines for Americans.* Washington, DC: US Government Printing Office; 1980. Home and Garden Bulletin No. 232.

5. World Health Organization Expert Committee. *Technical Report Series 678.* Geneva, Switzerland: World Health Organization; 1982.

6. Food and Nutrition Board, Division of Biological Sciences, Assembly of Life Sciences, National Research Council. *Toward Healthful Diets.* Washington, DC: National Academy of Sciences; 1980.

7. National Research Council, National Academy of Sciences. *Outlook for Science and Technology: The Next Five Years.* San Francisco, Calif: WH Freeman & Co; 1982.

8. American Council on Science and Health. *Diet Modification: Can It Reduce the Risk of Heart Disease?* New York, NY: American Council on Science and Health; 1982.

9. American Academy of Pediatrics, Committee of Nutrition. Prudent life-style for children: dietary fat and cholesterol. *Pediatrics.* 1986;78:521-525.

10. Samuel P, McNamara DJ, Shapiro J. The role of diet in the etiology and treatment of atherosclerosis. *Annu Rev Med.* 1983;34:179-194.

11. Ahrens EH. Eggs and cholesterol. *Lancet.* 1984;1:1127-1128.

12. Reiser R. A commentary on the rationale of the diet-heart statement of the American Heart Association. *Am J Clin Nutr.* 1984;40:654-661.

13. AMA Council on Scientific Affairs. Dietary and pharmacologic therapy for the lipid risk factors. *JAMA.* 1983;250:1873-1879.

14. US Dept of Health, Education, and Welfare. *National Center for Health Statistics Growth Charts.* Washington, DC: US Dept of Health, Education, and Welfare; 1976;25(No. 3 suppl):22. Monthly Vital Statistics Report.

15. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr.* 1981;34:2540-2545.

16. Keller W, Fulmore CM. Prevalence of protein-energy malnutrition. *World Health Stat Q.* 1983;36:129-167.

17. *Exchange Lists for Meal Planning.* New York, NY: The American Diabetes Association Inc, and Chicago, Ill: The American Dietetic Association; 1986.

18. *NutriQuest II. A Microcomputer-Based Nutrient Analysis System.* Kensington, Md: Capital Systems Group Inc; 1984.

19. *Lipid Research Clinics Population Studies Data Book, I: The Prevalence Study.* Washington, DC: Government Printing Office; 1980. US Dept of Health and Human Services publication NIH 80-1527.

20. National Institutes of Health Consensus Conference. Lowering blood cholesterol to prevent heart disease. *JAMA.* 1985;253:2080-2086.

21. Kwiterovich PO. Biochemical, clinical, epidemologic, genetic and pathologic data in the pediatric age group relevant to the cholesterol hypothesis. *Pediatrics.* 1986;78:349-362.

22. Dwyer J. Diets for children and adolescents that meet the dietary goals. *AJDC.* 1980;184:1073-1080.

23. Lifshitz F, Nishi Y. Mineral deficiencies during growth. In: Anast C, DeLuca H, eds. *Pediatric Diseases Related to Calcium.* New York, NY: Elsevier Science Publishing Co Inc; 1980:305-320.

24. Kagan A, Harris GR, Winkelstein W, et al. Epidemologic studies of coronary heart disease and strokes in Japanese living in Japan, Hawaii and California: demographics, physical, dietary and biochemical considerations. *J Chronic Dis.* 1974; 27:354-365.

25. Prasad AS. Clinical and biochemical spectrum of zinc deficiency in human subjects. In: Prasad AS, ed. *Clinical, Biochemical and Nutritional Aspects of Trace Elements.* New York, NY: Alan R Liss Inc; 1982:1-7.

26. Pugliese MT, Lifshitz F, Grad G, Marks-Katz M. Fear of obesity: a cause of short stature and delayed puberty. *N Engl J Med.* 1983;309:513-518.

27. Lifshitz F. Nutrition and growth. In: Paige DM, ed. *Clinical Nutrition: Nutrition and Growth Supplement.* St Louis, Mo: CV Mosby Co; 1985:40-47.

28. Pugliese MT, Weyman-Daum M, Moses N, Lifshitz F. Parental health beliefs as a cause of nonorganic failure to thrive. *Pediatrics.* 1987;80:175-182.

29. Lifshitz F, Moses N, Cervantes C, Ginsberg L. Nutritional dwarfing in adolescents. *Semin Adolesc Med.* 1987;3:255-266.

30. Dietz WH Jr, Hartung R. Changes in growth velocity of obese preadolescents during weight reduction. *AJDC.* 1985;139:705-707.

31. Weidman W, Kwiterovich P, Jesse MJ, Nugent E. Diet in the healthy child: Task Force Committee of the Nutrition Committee and the Cardiovascular Disease in the Young Council of the American Heart Association. *Circulation.* 1983; 69:1414A.

32. Conference on Blood Lipids in Children. Optimal levels for early prevention of coronary artery disease: workshop report, epidemiologic section, April 18 and 19, 1983, American Health Foundation. *Prev Med.* 1983;12:741-797.

33. Newman WP, Freedman DS, Voors AW, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa Heart Study. *N Engl J Med.* 1986;314:138-144.

34. Wynder EL, Berenson GS. Preventive strategies for reducing hyperlipidemia in childhood. *Prev Med.* 1984;13:327-329.

35. McNamara DJ. Diet and hyperlipidemia: a justifiable debate. *Arch Intern Med.* 1982; 142:1121-1124.

36. Ahrens EH. Diet and heart disease: shaping public perceptions when proof is lacking. *Arteriosclerosis.* 1982;2:856.

37. Sidney S, Farquhar JW. Cholesterol, cancer, and public health policy. *Am J Med.* 1983;75:494-508.

38. American Academy of Pediatrics, Committee on Nutrition. Toward a prudent diet for children. *Pediatrics.* 1983;71:78-80.

39. Nader PR, Taras HL, Sallis JF, Patterson TL. Adult heart disease prevention in childhood: a national survey of pediatricians' practices and attitudes. *Pediatrics.* 1987;79:843-850.

40. Hoeg JM, Brewer HB. Definition and management of hyperlipoproteinemia. *J Am Coll Nutr.* 1987;6:157-163.

41. West KM. Diabetes mellitus. In: Andersen LE, Coursin DB, Schneider HA, eds. *Nutritional Support of Medical Practice.* New York, NY: Harper & Row Publishers Inc; 1975:278-296.

42. West KM. Diet therapy of diabetes: an analysis of failure. *Ann Intern Med.* 1973;73:425-434.

Tracheobronchial Foreign Bodies

A Persistent Problem in Pediatric Patients

Heikki Puhakka, MD; Erkki Svedström, MD; Pentti Kero, MD; Päivi Valli, BM; Eila Iisalo, MD

• Extraction of a foreign body from the tracheobronchial tree was accomplished for 83 children. The mean age was 1 year 9 months for the 27 girls and 3 years 1 month for the 56 boys; 46 children (55%) were younger than 2 years of age. Sixteen (19%) of the foreign bodies were radiopaque, and 35 (42%) were either verified or suspected radiologically before endoscopy. Forty-one foreign bodies (49%) were situated in the right bronchial tree. Extraction was successful in 81 children (98%) and was performed on 50 children (60%) during the first 24 hours. Twenty-five (30%) of the foreign bodies were peanuts. Three children experienced a residual foreign body, without serious complications. We believe that an open tube bronchoscopy should be performed whenever abnormal stridor or cough is observed in a healthy child and when appropriate antibiotic therapy is unsuccessful.

(*AJDC*. 1989;143:543-545)

Inhalation of a foreign body is usually accompanied by severe coughing, stridor, wheezing, or dyspnea. This acute episode may escape the notice of the parents, and the cause may be obscured for a long period.[1] These acute symptoms may subsequently disappear, and an asymptomatic period may persist for several weeks.[2]

In spite of efforts to educate the public, aspiration of foreign bodies into the tracheobronchial tree still occurs, and infants and small children from the lower socioeconomic groups seem to suffer the most.[3] Usually, a rigid open bronchoscope has been used in the removal of the foreign bodies. During recent years a fiberoptic bronchoscope has been widely used in connection with pediatric endoscopy and also for removal of foreign bodies. However, for the removal of the aspirated foreign body, the open-tube bronchoscope with Hopkins telescopes is undoubtedly the instrument of choice.[1,3-7] Attempts to mobilize foreign bodies by inhalation of local decongestants, physiotherapeutic clapping, or postural drainage have had rather poor results.[8-10]

Foreign body aspiration may be hazardous or even fatal to the child. In some countries aspiration is a leading cause of in-home accidental deaths in children under 6 years of age.[11,12]

Radiology is the primary means of confirming the diagnosis. However, most foreign bodies are radiolucent. Chest roentgenograms of patients with foreign body aspiration have been evaluated as normal in as many as 15% to 35% of cases.[4,13] Roentgenographic findings of obstructive emphysema or atelectasis may be characteristic, but they are not always present.[13,14]

We reviewed our experience with tracheobronchial foreign bodies in 83 children during an 18-year period, and we report the retrospective analysis of this experience.

SUBJECTS AND METHODS

All pediatric patients with documented foreign body inhalation treated in our hospital during calendar years 1969 through 1987 are included in this retrospective analysis. Bronchoscopy was performed for a suspected or verified foreign body for 154 children; in 83 (54%) a foreign body was confirmed. The primary radiologic diagnosis was extracted from the radiologic reports in the hospital record.

The population served by the hospital is about 700 000. All pediatric endoscopic procedures are performed in the hospital.

General anesthesia, an open rigid bronchoscope, Hopkins telescopes, and optical forceps were used with all patients. Endoscopic removal of the foreign body, if necessary, was performed with fluoroscopic control. The flexible fiberoptic endoscope was used only occasionally.

There were 56 boys (67%) and 27 girls (33%), with a mean age of 2 years 10 months (3 years 1 month for boys and 1 year 9 months for girls). Twenty patients (24%) were under 1 year and 46 (55%) were under 2 years of age (Table 1).

RESULTS

Transient or persistent cough was the most common symptom (n = 64 [77%]). Thirty-one patients (37%) had signs of infection and 12 (14%) were cyanotic prior to endoscopy (Table 2).

In 77 children (93%), symptoms started suddenly and the parents were aware of them. In 27 children (33%), the time lag between inhalation and extraction of the foreign body was less than 12 hours, and in 50 children (60%), the extraction was performed within 24 hours (Table 3).

Radiologic examination prior to endoscopy demonstrated 16 radiopaque foreign bodies (19%) and evidence of bronchial obstruction by 19 foreign bodies (23%) (Table 4).

The lodgment sites of the foreign bodies are listed in Table 5. Forty-one foreign bodies (49%) were situated in the right and 25 (30%) in the left bronchial tree. The subglottis was the lodgment site in only 3 children.

A peanut was the most common foreign body (n = 25 [30%]). Twenty-four foreign bodies (29%) were of another organic origin (Table 6).

The endoscopic extraction was successful in 81 children (98%). In 3 children, 2 attempts on 2 subsequent days were needed to remove the foreign body. Thoracotomy was performed in

Accepted for publication December 30, 1988.

From the Departments of Otolaryngology (Dr Puhakka), Radiology (Dr Svedström), and Pediatrics (Drs Kero and Iisalo and Ms Valli) and University Central Hospital (Drs Puhakka, Svedström, Kero, and Iisalo and Ms Valli), Turku, Finland.

Reprint requests to Department of Otolaryngology, University Central Hospital, SF-20520 Turku, Finland (Dr Puhakka).

Table 1.—Age Distribution of Patients at Time of Foreign-Body Extraction

Age	Girls, %	Boys, %	Total, No. (%)
≤6 mo	4	0	1 (1)
7-12 mo	30	20	19 (23)
1-2 y	33	30	26 (31)
3-4 y	22	18	16 (19)
5-10 y	7	16	11 (13)
11-16 y	4	16	10 (12)
Total	**100**	**100**	**83 (100)***

*Percentages do not add to 100% because of rounding.

Table 2.—Symptoms Caused by Foreign Bodies (N=83)

Symptom	No. (%) of Patients
Cough	64 (77)
Stridor	51 (61)
Dyspnea	41 (49)
Fever	31 (37)
Cyanosis	12 (14)
No symptoms	5 (6)

Table 3.—Time Lag Between Inhalation of Foreign Body and Extraction (N=83)

Time Lag, d	No. of Patients	Time Lag, d	Cumulative No. (%) of Patients
≤1	50	≤1	50 (60)
2-3	7	0-3	57 (69)
4-7	9	0-7	66 (80)
8-14	7	0-14	73 (88)
≥15	10	0-210	83 (100)

Table 4.—Results of Clinical Radiologic Evaluation Before Endoscopy*

	No. (%)
Patients	84 (100)
Foreign bodies extracted	37 (44)
Radiologically suspected foreign bodies	35 (42)
True-positive findings in chest roentgenography compared with endoscopy	20/35 (57)
True-negative findings in chest roentgenography compared with endoscopy	32/49 (65)

*Patients whose radiologic reports were not available were excluded.

Table 5.—Lodgment Sites of Foreign Bodies (N=83)

Location	No. (%) of Patients
Subglottis	3 (4)
Trachea	10 (12)
Right bronchus	41 (49)
Main or stem bronchus	19 (23)
Lower-lobe bronchus	22 (27)
Left bronchus	25 (30)
Main bronchus	11 (13)
Lower-lobe bronchus	14 (17)
Both bronchi	3 (4)
Lung parenchyma	1 (1)

Table 6.—Nature of Aspirated Foreign Bodies (N=83)

Type of Foreign Body	No. (%) of Patients
Peanut	25 (30)
Apple	10 (12)
Pin or nail	9 (11)
Plastic material	9 (11)
Carrot	7 (8)
Other organic	7 (8)
Coin	3 (4)
Piece of stone	2 (2)
Miscellaneous	11 (13)

only 2 children. In a 13-year-old boy a pin was situated in the right-lower-lobe bronchus with the sharp end upward; it had perforated the bronchial wall. A piece of a spike had perforated the bronchial wall of another 13-year-old boy. A piece of a spike was lodged in the lung parenchyma of a third 13-year-old boy. There were only 3 cases of residual foreign bodies in this series, in 2 of which the first extraction was performed in another hospital. In one of these 2 children, a 2-year-old boy, the residual foreign body (peanut fragment) had been lodged in the left-lower-lobe bronchus for 5 months.

There were no deaths, cardiac arrests, or pneumothoraces associated with foreign body extraction in this series. In addition, no tracheostomies had to be performed. Reintubation was needed after the foreign body extraction in five children because of inspiratory stridor and hypoxia.

COMMENT

The success rate for the removal of inhaled tracheobronchial foreign bodies has reached 95% to 99%, mainly because of improvements in endoscopic equipment.[3-5,7] The development of optical forceps has made possible the extraction of foreign bodies located in peripheral sites. The Fogarty balloon technique and the Dormier basket have also been used successfully.[5] The removal of tracheal foreign bodies is the most dangerous.[15] In our series 13 children (16%) had a foreign body situated in the subglottis or trachea, but no complications occurred during extraction.

In many studies, including ours, the most common foreign body is a peanut. Extraction of a peanut may be difficult because of fragmentation or slippage, and residual foreign bodies may occur in up to 10% of the cases.[5] These residual foreign bodies may lodge in the bronchial tree for several weeks after the first extraction. In our series a residual foreign body was verified in 4% (3/83) of the cases, and all these children had recurrent pneumonia before the second extraction.

The inhaled foreign body should be removed as soon as the diagnosis is suspected or verified. Occult or radiolucent foreign bodies are sometimes difficult to locate and can present diagnostic difficulty. In cases with delayed diagnosis and infection, a distally located foreign body may be very difficult to visualize and extract. In such cases, antibiotic treatment and a repeated endoscopy after a few days should lead to a positive outcome. A very thin pin with the sharp end pointed upward may perforate the bronchial wall. In our patients, attempts were made to remove such a pin with the aid of the fiberoptic endoscope. The pin was too peripheral to be extracted from the bronchial wall, and thoracotomy was necessary.

Use of the rigid open bronchoscope with Hopkins telescopes is indicated in most cases, since the flexible fiberoptic endoscope (in connection with removal of the foreign body) has major drawbacks, particularly in small children.[3] The fiberoptic endoscope should be advanced through the rigid bronchoscope when removing small and/or peripheral foreign bodies to adequately control airways.

The diagnosis of foreign body aspiration may easily be missed by the examining physician,[5] especially when a typical history of aspiration is missing. In 77 (93%) of our children, the symptoms started suddenly and the parents were

aware of them. In several cases the parents believed that the foreign body had been spontaneously expelled by coughing, and the diagnosis was delayed. After an asymptomatic period of up to several weeks, bronchitis, wheezing, or fever related to the aspirated foreign body may be mistaken for acute bronchitis or an asthmatic episode.

If the child is not in acute respiratory distress, removal of the foreign body is not urgent and should be performed under proper conditions with adequate instruments.[9] Removal of the foreign body was performed during the first 12 hours in 27 (33%) and during the first 24 hours after inhalation in 50 (60%) of our children. Symptomatology may vary over an extremely wide range, from asymptomatic to severe dyspnea. During removal there may be abrupt changes for the worse, to severe asphyxia or cardiopulmonary arrest. This may be caused by a combination of hypoxia and reflex vagal stimulation.[5] In our children, no serious complications associated with foreign body extraction were experienced. This may be due to the fact that almost all foreign body extractions were performed by the same endoscopic team. Attempts at extraction should only be made by an experienced endoscopist with an armamentarium of different instruments and with the aid of a skilled anesthesiologic team. Only under emergency conditions, when the child is in danger of asphyxiation, should an attempt by a less-experienced endoscopist be permitted.

Although a foreign body was suspected in about two thirds of our patients, the correct radiologic diagnosis was established only in 52 (62%) of 84. Up to 75% of foreign bodies inhaled are radiolucent.[2] In our patient series, only 16 (19%) of the foreign bodies were radiopaque. In these patients the radiologic diagnosis is straightforward, and precise localization is possible. Difficulties are encountered when the foreign body is radiolucent and the interval between inhalation and radiologic evaluation is short, because the physiologic reactive changes are not yet evident on chest roentgenograms. In 7 of 12 false-negative cases, inspiration and expiration roentgenograms showed no abnormalities. The other 5 patients showed multiple atypical pulmonary densities that were incorrectly diagnosed as pulmonary infection on admission. False-positive or false-negative diagnosis may also occur when the patient has a concomitant pulmonary infection.

The new radiologic imaging modalities (isotope methods, computed tomography) have not improved diagnostic accuracy. The role of digital subtraction techniques, allowing objective evaluation of fluoroscopic images, remains to be defined.[16,17]

We thank Peter Dean, MD, Department of Diagnostic Radiology, Turku (Finland) University Central Hospital, for reviewing the manuscript.

References

1. Puhakka H, Kero P, Erkinjuntti M. Pediatric bronchoscopy during a 17-year period. *Int J Pediatr Otorhinolaryngol*. 1987;13:171-180.
2. Kero P, Puhakka H, Erkinjuntti M, Jisalo E, Vilkki P. Foreign body in the airway of children. *Int J Pediatr Otorhinolaryngol*. 1983;6:51-59.
3. Weissberg D, Schwartz I. Foreign bodies in the tracheobronchial tree. *Chest*. 1987;91:730-733.
4. Blazer S, Naveh Y, Friedman A. Foreign body in the airway. *AJDC*. 1980;134:68-71.
5. Kosloske AM. Bronchoscopic extraction of aspirated foreign bodies in children. *AJDC*. 1982; 136:924-927.
6. Wood RE. Spelunking in the pediatric airways: explorations with flexible fiberoptic bronchoscope. *Pediatr Clin North Am*. 1984;31:785-799.
7. Mantel K, Butenandt I. Tracheobronchial foreign body aspiration in childhood: a report on 224 cases. *Eur J Pediatr*. 1986;145:211-216.
8. Law DK, Kosloske AM. Management of tracheobronchial foreign bodies in children: a re-evaluation of postural drainage and bronchoscopy. *Pediatrics*. 1976;58:362-367.
9. Stool SE, Bluestone CD. You have to use endoscopy. *Pediatrics*. 1978;61:145-146.
10. Bready LL, Orr MD, Petty C, Grover FL, Harman K. Bronchoscopic administration of nebulized racemic epinephrine to facilitate removal of aspirated peanut fragments in pediatric patients. *Anesthesiology*. 1986;65:523-525.
11. Black RE, Choi KJ, Syme WC, Johnson DG, Matlak ME. Bronchoscopic removal of aspirated foreign bodies in children. *Am J Surg*. 1984;148:778-781.
12. Musemeche CA, Kosloske AM. Normal radiography findings after foreign body aspiration. *Clin Pediatr*. 1986;25:624-625.
13. Gaafar H, Abdel-Ayem M, Talaat M, Mandour M. The value of x-ray examination in the diagnosis of tracheobronchial foreign bodies in infants and children. *ORL J Otorhinolaryngol Relat Spec*. 1982;44:340-348.
14. Wesenberg RL, Blumhagen JD. Assisted expiratory chest radiography: an effective technique for the diagnosis of foreign-body aspiration. *Radiology*. 1979;130:538-539.
15. Esclamado RM, Richardson MA. Laryngotracheal foreign bodies in children: a comparison with bronchial foreign bodies. *AJDC*. 1987;141: 259-262.
16. Bacques O, Chereau O, Dumouchel M. A study of pulmonary ventilation in children using digital subtraction fluoroscopy. *Medicamundi*. 1983;28:77-84.
17. Schmit P, Faure C, Sardet A, Bacques O. Pulmonary ventilation in children: digital subtraction study. *Ann Radiol*. 1985;28:308-314.

In Other AMA Journals

JAMA

Cryotherapy in Infants With Retinopathy of Prematurity
D. L. Phelps, C. E. Phelps (*JAMA*. 1989;261:1751-1756)

Classification and Analysis of Fetal Deaths in Massachusetts
E. J. Lammer; L. E. Brown; M. T. Anderka; B. Guyer (*JAMA*. 1989;261:1757-1762)

Pediatric Coin Ingestions

A Prospective Study of Coin Location and Symptoms

Jeff E. Schunk, MD; Howard Corneli, MD; Robert Bolte, MD

• Coins are the most common esophageal foreign body in children. We prospectively evaluated 52 consecutive children who had swallowed coins to determine the incidence of asymptomatic esophageal coins and the rate of spontaneous passage. All patients had a roentgenogram; coins were removed from the esophagus if the patient was symptomatic. Children with asymptomatic esophageal coins were allowed less than 24 hours to pass the coin to the stomach. Thirty children had esophageal coins; of these, 9 (30%) were asymptomatic. The presence of symptoms was significantly associated with esophageal coins, but the absence of symptoms did not reliably exclude the possibility of an esophageal coin. All children who swallow coins should undergo roentgenographic evaluation.

(*AJDC*. 1989;143:546-548)

Coins are frequently swallowed by children[1-3] and account for the majority of esophageal foreign bodies.[1,4-6] If the coin passes to the stomach it will generally pass through the remainder of the gastrointestinal tract without any problems.[1,3,7] Coins that lodge in the esophagus may cause several serious complications, including airway obstruction,[8] esophageal perforation,[9] esophageal-aortic fistula,[10] and tracheoesophageal fistula.[11] Esophageal coins that cause symptoms should obviously be removed. Because of the serious nature of the complications from coins that remain lodged in the esophagus, it is also recommended that *all* coins (symptomatic or not) be removed.[1,2,4,5,8,12,13]

See also pp 529 and 549.

Can the physician determine clinically which patients have a coin lodged in the esophagus? In a review of esophageal foreign bodies that included 343 children, it was noted that children usually have symptoms of refusal to take foods, increased salivation, pain or discomfort on swallowing, or vomiting.[12] There was no mention of children with esophageal foreign bodies who were asymptomatic.[12] A retrospective study of 88 patients (mostly children) admitted for removal of esophageal foreign bodies showed that though dysphagia was common (42%), 18.2% of the patients were asymptomatic.[5] In another retrospective review of children who swallowed coins, 11 of 25 children with an esophageal coin were asymptomatic in the emergency department (ED).[14] Therefore, it has been recommended that *all* children who swallow coins should have roentgenograms taken to determine the location of the coin.[14]

It was our impression that this was not common practice in our community. A telephone survey of 65 practicing pediatricians in the Salt Lake City, Utah, area in the fall of 1985 revealed that 77% would not take a roentgenogram of a child who was asymptomatic after swallowing a coin. Several hypotheses might explain this variance between the medical literature and actual practice. Retrospective reviews may have missed symptoms and falsely inflated the number of "asymptomatic" esophageal coins. Alternatively, individual pediatricians may not treat enough cases to discover complications when the true incidence of complications is small. Finally, asymptomatic esophageal coins might later pass spontaneously to the stomach. We conducted a prospective study to determine the incidence of asymptomatic esophageal coins and the rate of spontaneous passage from the esophagus.

METHODS

Following approval from the Primary Children's Medical Center (Salt Lake City) Human Subjects Committee, all patients who presented consecutively to Primary Children's Medical Center ED between April 10, 1986, and May 1, 1987, with a complaint of coin ingestion were evaluated. Symptoms at ingestion and symptoms and physical findings in the ED were recorded. All children underwent roentgenographic evaluation. Most children underwent a "foreign-body search," consisting of a lateral soft-tissue neck roentgenogram and a posteroanterior view that included the oropharynx, neck, chest, and abdomen (this was the study preferred by our Radiology Department for the evaluation of a swallowed foreign body). Patients referred for removal of coins lodged in the esophagus underwent fluoroscopy to facilitate the removal described below.

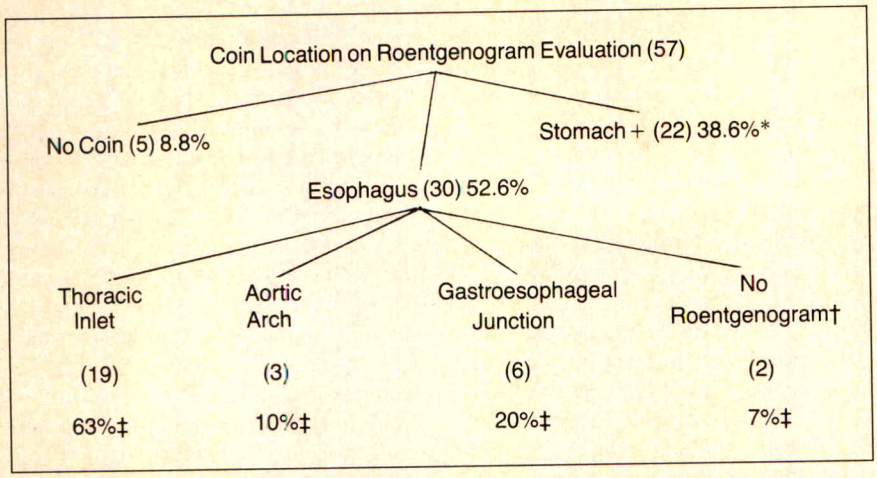
Coins in the stomach were allowed to pass. Coins in the esophagus were removed if the patient was symptomatic; otherwise, informed consent was sought and the patient was discharged and allowed up to 24 hours for the coin to pass to the stomach. Patients were not eligible for this waiting period if the coin ingestion occurred more than 24 hours prior, if the child was referred specifically for coin removal, if the child was unable to take

Accepted for publication February 10, 1989.

From the Division of Emergency Medicine, Childrens Hospital of Los Angeles (Calif) (Dr Schunk); and Department of Pediatrics, Primary Children's Medical Center, University of Utah Medical Center, Salt Lake City (Drs Corneli and Bolte).

Presented at the 28th Annual Meeting of the Ambulatory Pediatric Association, May 3, 1988, Washington, DC.

Reprint requests to Division of Emergency Medicine, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Schunk).



The location of a swallowed coin on roentgenographic evaluation in 57 children presenting to the emergency department with a complaint of a swallowed coin. The number of patients in each category are in parentheses. Asterisk indicates the coin was located in the stomach or a more distal gastrointestinal tract; dagger, a roentgenogram was obtained and the location was identified as "esophagus," but it was unavailable for review; and double dagger, the percent of the esophageal coins.

Table 1.—Symptoms in the Emergency Department and Coin Location*

Symptoms	Coin Location, No. of Patients: Esophagus	Stomach +†
Dysphagia/ drooling	12	0
Pain	7	5
Localization	5	3
Vomiting	5	0
Cough	2	0
Stridor	1	0

*All five patients in whom no coin was seen on roentgenography were asymptomatic in the emergency department.

†Roentgenogram showed coin located in stomach or further in gastrointestinal tract.

Table 2.—Presence of Symptoms in the Emergency Department and Coin Location*

	Coin Location: Esophagus	Not Esophagus	Total
Symptoms Yes	21	5	**26**
No	9	17†	**26**
Total	**30**	**22**	**52**

*$\chi^2 = 9.53$; $P < .005$.

†This number does not include the five asymptomatic children in whom no coin was demonstrated on roentgenographic examination.

liquids or solids in the ED, or if the child had a history of esophageal disease or surgery.

Coins were removed by a radiologist under fluoroscopic guidance using the Foley catheter technique.[15,16] All roentgenograms involving esophageal coins were reviewed by one of us (J.E.S.) to further specify the coin location within the esophagus as at the thoracic inlet, the level of the aortic arch, or the gastroesophageal junction.

Data analyses were done using standard statistical methods, including χ^2 analysis.

RESULTS

There were 57 children (36 boys and 21 girls) entered into the study with ages ranging from 7 months to 11 years (mean, 3.5 years). No child had a history of esophageal disease or surgery. Two children had a history of a previous esophageal foreign body (one coin and one fish bone).

The location of the coin on roentgenogram is shown in the Figure. In five children there was no coin evident on roentgenogram, though the child was brought in for suspected coin ingestion. Two roentgenograms were unavailable for review, though "esophagus" was marked on the data sheet.

The number of children with specific symptoms in the ED and the coin location on roentgenogram are shown in Table 1. Drooling or dysphagia was the most common symptom in those children with an esophageal coin and was not present in any of the children with coins in the stomach. All five children with no coin demonstrated on roentgenogram were asymptomatic. These five children were not included in the statistical analysis below.

Table 2 compares the presence or absence of symptoms in the ED and coin location on roentgenogram (in the esophagus or more distal in the gastrointestinal tract). Analysis of this 2×2 table yielded $\chi^2 = 9.53$ ($P < .005$). The presence of symptoms in the ED as a test for an esophageal coin had a sensitivity of 70%, a specificity of 77%, a positive predictive value of 81%, and a negative predictive value of 65%.

Nine children without symptoms demonstrated an esophageal coin on roentgenogram. These children were potentially eligible for the waiting period to allow the coin to pass from the esophagus. Two, however, were referred to the ED specifically for removal (so the coin was removed) and two others were not entered because the parents declined to give consent for the waiting period (so the coin was removed). An additional two children had the coin removed at initial presentation due to failure to follow the study protocol. The remaining three children passed the coin from the esophagus as seen on follow-up roentgenograms done after waiting from 3 to 20.5 hours.

There were 30 children with an esophageal coin. Twenty-three of these children had the coin removed using the Foley catheter technique. In one child with a 5-day history of noisy breathing, Foley catheter removal failed and the coin was removed by esophagoscopy. Another child, who had an apneic episode during attempted esophagoscopy at another hospital, immediately underwent esophagoscopy in the operating room. Five children spontaneously passed the coin to the stomach (three of these were asymptomatic cases mentioned above, while two were symptomatic but passed the coin while waiting to have the coin removed).

There were 25 coins recovered from the esophagus. Of these, there were 17 pennies, 3 quarters, 2 dimes, 2 nickels,

and 1 video game token the size of a nickel.

COMMENT

Our results are similar to those previously published regarding the age of the children who either swallow coins or have demonstrated esophageal coins.[3-5,13,14] The anatomic distribution of the esophageal coins is similar to other reports of esophageal foreign bodies.[3,5,12] Pennies were the most frequent esophageal coin in our study, in agreement with others.[14,15,17] This probably represents the frequency with which pennies are accessible to children rather than any consideration of esophageal anatomy and coin size.

The presence of any symptom at the time of evaluation will often predict the presence of an esophageal coin. This is shown by a positive predictive value of 81% as 21 of the 26 symptomatic children proved to have esophageal coins. The most common symptoms in the children with esophageal coins were dysphagia or drooling, vomiting, pain, and localization. This symptom list was almost identical to that found in other studies.[5,12,14,18] The absence of symptoms on presentation, however, does not rule out an esophageal coin as reflected in the low (65%) negative predictive value. This reflects the fact that 9 (35%) of 26 asymptomatic children who ingested a coin proved to have the coin lodged in the esophagus. Since symptoms or their absence cannot accurately predict the location of a swallowed coin, we recommend that children who swallow coins should undergo roentgenographic examination.

Clearly some esophageal coins will pass to the stomach. In this study all three of the asymptomatic children who underwent a waiting period passed the coin from the esophagus, and so did two of the symptomatic children waiting for removal (<4 hours). In the study conducted by Hodge et al,[14] 10 of 25 children with esophageal coins passed the coin to the stomach in 1 to 5 hours. In Spitz's[3] review of 205 esophagoscopies for esophageal foreign bodies in children, there was a 19% incidence of negative endoscopy, presumably many due to spontaneous passage during or before the procedure.

When passage to the stomach does not spontaneously occur, the child is at risk for complications. In Nandi and Ong's[12] review of 2394 esophageal foreign bodies (343 in children), there were 25 perforations (only 1 in a child, which was secondary to a fish bone) and those that were not due to instrumentation occurred after 24 hours. Most were caused by sharp foreign bodies. Despite these results, they recommended removal "as soon as the diagnosis is made."[12] Spitz[3] recommends that objects in the lower third of the esophagus be observed for up to 12 hours since 72% of these patients with these foreign bodies had negative endoscopies. The esophageal aortic fistula reported by Vella and Booth[10] occurred after 1 week of impaction, and in this case, the coin was composed of a "central iron core coated with an alloy of copper and zinc," which may be more corrosive than coins used today in the United States. The other reports of serious complications from esophageal coins in children have occurred after impactions lasting 3 months,[8] 4 months,[9] 6 months,[3] and 8 years.[11] There were two impactions of at least 5 days' duration in our study. Neither coin caused a perforation, but mucosal erosion was seen at esophagoscopy in one case, and in the other, the coin edges were completely embedded in the mucosa.

It may be that 24 hours from the time of ingestion represents a safe period of observation in a child with an asymptomatic esophageal coin where good follow-up is assured. Other authors have also suggested that observation may be prudent in selected cases of esophageal foreign bodies.[2,5] The number of patients enrolled in this aspect of the study was too small to draw conclusions. Some of the parents felt inconvenienced by a return visit to the ED and preferred to have the coin removed at the initial visit. At other institutions where an operative procedure (rather than the Foley catheter technique) is utilized for removal, this "inconvenience" might be more readily accepted. If future investigations support delayed evaluation in the asymptomatic children, this will spare some the discomfort, risk, and expense of removal. The degree of the discomfort and risk and the cost of removal would vary depending on the method of removal. Additional study of children with asymptomatic esophageal coins is necessary to further delineate the efficacy and confirm the safety of delaying removal for up to 24 hours.

The best removal method for blunt esophageal foreign bodies is controversial. There are advocates for the use of rigid endoscopy,[1-3,6,12,19] flexible endoscopy,[18] Foley catheters,[5,13,15,16] and now bougie dilator advancement.[17] The Foley catheter technique (performed by the radiologist under fluoroscopic guidance) has been the method of choice for many years at the study institution. This study was designed to investigate the detection of esophageal coins; it was not the purpose of this study to investigate or compare methods of removal.

References

1. Binder L, Anderson WA. Pediatric gastrointestinal foreign body ingestions. *Ann Emerg Med.* 1984;13:112-117.
2. Gracia C, Frey CF, Balaz IB. Diagnosis and management of ingested foreign bodies: a ten year experience. *Ann Emerg Med.* 1984;13:30-34.
3. Spitz L. Management of ingested foreign bodies in childhood. *Br Med J.* 1971;4:469-472.
4. Baraka A, Bikhazi G. Oesophageal foreign bodies. *Br Med J.* 1975;1:561-563.
5. Chaikhouni A, Kratz JM, Crawford FA. Foreign bodies in the esophagus. *Am Surg.* 1985; 51:173-179.
6. Giordano A, Adams G, Boies L Jr, Meyerhoff W. Current management of esophageal foreign bodies. *Arch Otolaryngol Head Neck Surg.* 1981;107:249-251.
7. Pellerin D, Fortier-Beaulieu M, Gueguen F. The fate of swallowed foreign bodies: experience of 1250 instances of sub-diaphragmatic foreign bodies in children. *Prog Pediatr Radiol.* 1969;2:286-302.
8. Pasquariello PS, Kean H. Cyanosis from a foreign body in the esophagus. *Clin Pediatr.* 1975;14:223-225.
9. Nahmah BJ, Mueller C. Asymptomatic esophageal perforation by a coin in a child. *Ann Emerg Med.* 1984;13:627-629.
10. Vella EE, Booth PJ. Foreign body in the oesophagus. *Br Med J.* 1965;2:1042.
11. Obiako MN. Tracheoesophageal fistula: a complication of foreign body. *Ann Otol Rhinol Laryngol.* 1982;91:325-327.
12. Nandi P, Ong GB. Foreign body in the oesophagus: review of 2394 cases. *Br J Surg.* 1978;65:5-9.
13. O'Neill JA, Holcomb GW, Neblett WW. Management of tracheobronchial and esophageal foreign bodies in childhood. *J Pediatr Surg.* 1983;18:475-479.
14. Hodge D III, Tecklenburg F, Fleisher G. Coin ingestion: does every child need a radiograph? *Ann Emerg Med.* 1985;14:443-446.
15. Bigler FC. The use of a Foley catheter for removal of blunt foreign bodies from the esophagus. *J Thorac Cardiovasc Surg.* 1966;51:759-760.
16. Carlson D. Removal of coins in the esophagus using a Foley catheter. *Pediatrics.* 1972;50:475.
17. Bonadio WA, Jona JZ, Glicklich M, Cohen R. Esophageal bougienage technique for coin ingestion in children. *J Pediatr Surg.* 1988;23:917-918.
18. Bendig DW. Removal of blunt esophageal foreign bodies by flexible endoscopy without general anesthesia. *AJDC.* 1986;140:789-790.
19. Ritter FN. Questionable methods of foreign body treatment. *Ann Otol Rhinol Laryngol.* 1974;83:729-733.

Pediatric Coin Ingestion

A Prospective Study on the Utility of Routine Roentgenograms

E. Martin Caravati, MD; Don L. Bennett, RPh; Newell E. McElwee, PharmD

• It has been recommended that all children with a history of coin ingestion immediately undergo roentgenography to locate the coin, regardless of symptoms. We performed a prospective evaluation of these ingestions to determine the risk of asymptomatic esophageal impaction and the need for routine roentgenography. One hundred sixty-two children (mean ± SD age, 3.6 ± 2.1 years) were evaluated. All were referred for immediate roentgenography after ingestion and followed up daily by telephone for 5 days. Sixty-six patients (41%) did comply and 96 (59%) did not comply with the roentgenogram recommendation. A coin was visualized in the esophagus of 13 patients (20%); 11 were symptomatic and 2 were asymptomatic at the time of ingestion. Symptomatic patients had a 42% risk of a coin later being located in the esophagus compared with a 5% risk for asymptomatic patients. The asymptomatic patients with lodged coins passed them without difficulty after the administration of oral fluids. Nineteen percent of the patients who did not undergo roentgenography were symptomatic and all became asymptomatic within 24 hours of ingestion. There was no difference in morbidity between the group that underwent roentgenography and the group that did not undergo roentgenography at 5 days after ingestion. Children who are asymptomatic at the time of coin ingestion may not need routine roentgenography if they can tolerate oral fluids and telephone follow-up is available.

(*AJDC.* 1989;143:549-551)

Accepted for publication December 19, 1988.

From the Intermountain Regional Poison Control Center (Drs Caravati, Bennett, and McElwee) and the Division of Emergency Medicine, University of Utah School of Medicine (Dr Caravati), Salt Lake City, Utah.

Presented at the American Association of Poison Control Centers, American Academy of Clinical Toxicology, American Board of Medical Toxicology, and Canadian Association of Poison Control Centers Annual Meeting, Baltimore, Md, October 2, 1988.

Reprint requests to Emergency Department, University Hospital, 50 N Medical Dr, Salt Lake City, UT 84132 (Dr Caravati).

Ingestion of coins by children is frequently the reason for calls to poison control centers in the United States. More than 2800 cases were reported by the American Association of Poison Control Centers Database in 1987.[1] Recently, it has been suggested that all patients who ingest a coin should undergo roentgenography to locate the coin, regardless of symptoms.[2,3] The rationale for this recommendation is based on a reportedly high incidence of asymptomatic lodged esophageal coins that may go undetected and, therefore, result in unnecessary complications.[3]

See also pp 529 and 546.

We undertook a prospective evaluation of pediatric coin ingestions to determine the risk of a coin being lodged in the esophagus of asymptomatic vs symptomatic children at the time of ingestion, and to assess the utility of obtaining a roentgenogram for all patients, regardless of symptoms.

METHODS

The Intermountain Regional Poison Control Center, Salt Lake City, Utah, is staffed 24 hours a day by pharmacists who specialize in poison information. The center serves a population base of over 1.5 million people and has a penetrance of approximately 20 calls per 1000 population. From October 1, 1985, to March 1, 1988, all coin ingestions reported to the poison control center were prospectively studied. Patient age, sex, symptoms at time of ingestion, type of coin, time of ingestion, and follow-up telephone number were recorded. All patients were referred to a health care facility to obtain a chest roentgenogram (including cervical esophagus) immediately after the call.

Follow-up inquires were made within 6 hours of the call to determine whether a radiograph had been obtained, its results, and any subsequent treatment rendered. To detect any recurrence of symptoms or complications from the ingestion, each patient was followed up daily by telephone for at least 5 days after ingestion or until the coin passed in the stool. The poison control center did not recommend any therapy before obtaining the roentgenogram. Patients were excluded from the study for age greater than 12 years, a history of coingestants requiring gastric emptying, or inability to follow up the case.

Statistical analysis was performed using Epiinfo software (Division of Surveillance and Epidemiologic Studies, Epidemiology Program Office, Centers for Disease Control, Atlanta, Ga). Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous exposure variables, including symptoms (ever, never), age (≤3 years, >3 years), sex, and coin size (quarter, other), and the dichotomous outcome variable of radiographic location of the coin (esophagus, not in esophagus). A 95% CI that does not include 1.0 is considered statisically significant at an α value of .05.

RESULTS

One hundred sixty-two consecutive cases of pediatric coin ingestion were evaluated during the 28-month study period. No cases were excluded. The mean patient age was 3.5 ± 2.1 years (range, 9 months to 12 years). Fifty-six percent of the patients were boys and 44% were girls. None of the patients had a history of esophageal disease.

Symptoms at the time of ingestion were reported in 44 patients (27%) and included chest or throat pain in 24 patients, choking or gagging in 13 patients, vomiting in 8 patients, and nonspecific complaints in 2 patients. Some patients reported more than one symptom. The duration of symptoms varied from minutes to hours in this group. No symptoms were reported in 118 patients (73%) at the time of ingestion and all of them remained asymptomatic throughout the 5-day follow-up period.

Roentgenographic Location of Coin Compared With Presence of Symptoms at Time of Ingestion*

	Symptoms	No Symptoms	Total
Esophagus	11	2	13
Not in esophagus	15	38	53
Total	**26**	**40**	**66**

*The risk ratio = (11/26)/(2/40) = 8.5; 95% confidence interval, 2.0 to 35.1.

Sixty-six patients (41%) complied with poison control center recommendations and underwent roentgenography within 6 hours of ingestion. Of these patients, 26 (39%) were symptomatic at the time of ingestion and 40 (61%) were asymptomatic. In 41 patients (62%), the coin was visualized in the stomach or intestinal tract. A coin was not seen in 12 patients (18%). A coin was seen in the esophagus of 13 patients (20%); 11 were symptomatic and 2 were asymptomatic (Table).

The symptomatic patients faced a 42% risk of a coin later being located in the esophagus by roentgenography, while asymptomatic patients faced a 5% risk. Symptomatic patients were 8.5 times more likely (95% CI, 2.0 to 35.1) for a coin to be visualized in the esophagus than asymptomatic patients. In the two asymptomatic patients with lodged coins, the coin was visualized at the gastroesophageal junction and passed spontaneously after the administration of liquids in the emergency department. Three symptomatic patients had the coin removed by esophagoscopy within 2 hours of presentation to the emergency department. The remaining eight patients passed the coin into the stomach spontaneously with the administration of oral fluids.

Of the 13 lodged coins, 4 were quarters, 3 were nickels, 5 were pennies, and 1 was a dime. Patients ingesting quarters were more likely than patients ingesting other coins to develop symptoms (RR = 2.5; 95% CI, 1.6 to 4.0) or to have a coin located in the esophagus at roentgenographic examination (RR = 3.8; 95% CI, 1.5 to 9.0). The mean age of patients with a coin located in the esophagus was 3.7 ± 2.0 years (median age, 3.0 years), and the mean age for other patients undergoing roentgenography was 2.9 ± 2.0 years (median age, 2.0 years). Patients older than 3 years were equally as likely as younger patients (RR = 2.0, 95% CI, 0.8 to 5.1), and boys were equally as likely as girls (RR = 1.4, 95% CI, 0.5 to 4.0), to have a coin located in the esophagus at the time a roentgenogram was obtained.

In 96 (59%) of 162 cases, a roentgenogram was not obtained despite strong recommendations by the poison control center staff. Eighteen (19%) of these patients were symptomatic at the time of ingestion and all became asymptomatic within 24 hours. There were no symptoms or morbidity reported at the 5-day follow-up in either the group that underwent roentgenography or the group that did not undergo roentgenography.

COMMENT

Over the past several years, recommendations have been made to perform roentgenography in all patients with a history of foreign-body ingestion, regardless of symptoms. In 1983, Bailey[4] reported the case of a 5-year-old girl who swallowed a plastic button and was asymptomatic for 24 hours, then presented with throat pain and a refusal to eat. The 2.5-cm plastic button was found lodged at the level of the cricopharyngeus muscle 6 days later. Based on this case, she recommended that an anteroposterior and lateral roentgenogram of the neck be obtained for every patient with a history of foreign-body ingestion and that a barium swallow be considered, even if the patient is asymptomatic.

In a retrospective analysis of pediatric foreign-body ingestions, Binder and Anderson[2] found that a significantly higher percentage of foreign-body esophageal impaction cases (60%) managed with Foley catheter extraction or endoscopy involved ingested coins rather than other objects. They concluded that all cases of suspected foreign-body ingestion should have roentgenographic evaluation and that coins had an uniquely high predilection for esophageal impaction.

In 1985, Hodge and associates[3] limited their study to pediatric coin ingestions and attempted to define the indications for roentgenography. They retrospectively evaluated 80 patients presenting to an emergency department with the chief complaint of having "swallowed a coin." Fifty-two (65%) of these patients were asymptomatic at the time of ingestion and 7 (14%) were found to have a coin lodged in the esophagus. Based on these results, Hodge and associates also recommended that all children with a history of coin ingestion receive a chest roentgenogram regardless of symptoms, and suggested that it was unwise to give advice over the telephone to such patients.

We prospectively evaluated 162 children with a history of coin ingestion and found that there is a 5% risk of having a lodged esophageal coin in a patient asymptomatic at the time of ingestion. These patients passed the coin into the stomach without difficulty after the administration of oral fluids. If our estimate is accurate, then obtaining routine roentgenograms on all asymptomatic patients with a history of coin ingestion would result in the vast majority, if not all, of them receiving unnecessary ionizing radiation and unwarranted medical expenses. The ability of the patient to tolerate oral liquids without difficulty may be the key to allowing observation at home without referral for a roentgenogram. All of our patients who did not undergo roentgenography were able to tolerate liquids at home and there was no morbidity reported during their observation period. We chose a 5-day observation period because 99% of gastric foreign bodies will pass through the entire gastrointestinal tract during this time.[5]

The indications for endoscopic removal of the coin within 2 hours of presentation to the emergency department in three symptomatic cases was unclear. There was no reported evidence of respiratory compromise in these patients, and the exact location of the coin was not reported. It is not known whether a longer observation period or administration of fluids would have resulted in spontaneous passage of these coins. The eight other symptomatic and two asymptomatic patients found to have impacted esophageal coins passed them into the stomach without difficulty after the administration of oral fluids. The 12 patients for whom a coin was not visualized on roentgenography may not have actually ingested a coin or the coin may

have moved so rapidly along the gastrointestinal tract that it was not included in the area seen on roentgenography.

Compliance with the poison control center recommendation to obtain a roentgenogram was low in all patients. Fifty-nine percent of our patients subsequently contacted their private physician or local emergency department, were instructed not to have roentgenography performed, and were observed at home. Nineteen percent of them were symptomatic at the time of ingestion; all were able to tolerate liquids and became asymptomatic within 24 hours. At the 5-day follow-up, there was no difference in morbidity between the group that underwent roentgenography and the group that did not undergo roentgenography.

Our patient population differs from those of previous studies in that we prospectively studied calls from patients at home concerning exposure rather than retrospectively evaluating emergency department patient records. We feel that our patient population is more representative of one that a pediatrician is likely to encounter when receiving calls from parents for advice. Our study is limited in that recurrence of symptoms or complications after the 5-day follow-up period would not have been detected. It suggests, however, that children with a history of coin ingestion who are asymptomatic at home need not immediately undergo roentgenography as long as they can tolerate oral fluids without difficulty and close follow-up by telephone is available.

References

1. Litovitz TL, Schmitz BF, Matyunas N, Martin TG. 1987 annual report of the American Association of Poison Control Centers National Data Collection System. *Am J Emerg Med.* 1988;6:479-515.
2. Binder L, Anderson WA. Pediatric gastrointestinal foreign body ingestions. *Ann Emerg Med.* 1984;13:112-117.
3. Hodge D, Tecklenburg F, Fleisher G. Coin ingestion: does every child need a radiograph? *Ann Emerg Med.* 1985;14:443-446.
4. Bailey P. Pediatric esophageal foreign body with minimal symptomatology. *Ann Emerg Med.* 1983;12:452-454.
5. Pellerin D, Fortier-Beaulieu M, Gueguen J. The fate of swallowed foreign bodies: experience of 1250 instances of subdiaphragmatic foreign bodies in children. *Prog Pediatr Radiol.* 1969;2:286-302.

Book Review

Textbook of Critical Care, 2nd ed, edited by W. C. Shoemaker, S. Ayres, A. Grenvik, et al, $96.25, Philadelphia, Pa, WB Saunders Co, 1988.

Since the first edition of the Society of Critical Care Medicine's *Textbook of Critical Care* was published in 1984, critical care medicine has emerged as a recognized subspecialty in the disciplines of pediatrics, surgery, anesthesiology, and internal medicine. The American Board of Pediatrics certified its first cohort of pediatric critical care medicine specialists in 1987. Pediatric critical care is expanding as a clinical, teaching, and research discipline in the 1980s, much as neonatology expanded in the late 1960s and early 1970s. There has been a concomitant proliferation of related textbooks.

Oftentimes, second editions of textbooks are merely updates of the previous edition. Happily, these editors were far more ambitious. This edition is better organized and written. The first edition exhibited the marked unevenness in style and content that plagues many multiauthored textbooks. These editors clearly molded the second edition into a more cohesive textbook. The number of chapters has increased from 123 to 164, and the text is almost 50% longer. An entire six-chapter section on transplantation has been added as well as a five-chapter section on nursing care. Our modern era has demanded new chapters on acquired immunodeficiency syndrome, radiation poisoning, and extracorporeal membrane oxygenation in neonates. Chapters addressing the medical and legal aspects of brain death and forgoing life-sustaining treatment are succinct, well written, and informative.

Since the first edition of *Textbook of Critical Care* was published, two new pediatric intensive care books have been published: *Textbook of Pediatric Intensive Care* by Rogers[1] and *Pediatric Intensive Care* by Morray.[2] Pediatric house officers and pediatricians would find each of these textbooks useful. Rogers' is the most comprehensive textbook of pediatric critical care; Morray's is the most concise. The *Textbook of Critical Care* is more current.

It is the most comprehensive textbook on adult and pediatric critical care. It is well referenced and contains 28 chapters dedicated to pediatric and neonatal topics. Which of these textbooks would be most useful depends on the needs of the reader. Certainly, most pediatrician intensivists will want to add the new edition of *Textbook of Critical Care* to their personal libraries.

ROBERT A. BERG, MD
Pediatric Critical Care
Arizona Health Sciences Center
1501 N Campbell Ave
Tucson, AZ 85724

1. Rogers MC, ed. *Textbook of Pediatric Intensive Care.* Baltimore, Md: Williams & Wilkins; 1987;1,2.
2. Morray JP. *Pediatric Intensive Care.* Norwalk, Conn; Appleton & Lange; 1987.

Physiotherapy for Children With Cerebral Palsy

Evidence for Its Efficacy

Emanuel Tirosh, MD, Sheri Rabino, MSc

• Physiotherapy is currently the most popular therapeutic intervention for cerebral palsy. This therapy requires highly trained personnel, diverse equipment, and parental cooperation. Notwithstanding the expense and commitment required for the implementation of a therapeutic program, a computer search of the literature published in English during the past 15 years revealed only nine studies pertaining to the efficacy and no study addressing the effectiveness of this intervention. A critical review of this literature, employing 14 methodological and reporting criteria, revealed that only three studies adequately fulfilled nine of the criteria; the remaining studies used a less rigorous design. Of those three articles, two used statistical analysis and concluded that the results were negative, while the third utilized clinical analysis only and demonstrated positive results. Evidence for the usefulness of this therapy has yet to be demonstrated; with the presently available methodologies it is ethically imperative to institute a properly designed, collaborative, multicenter, randomized, controlled trial.

(*AJDC*. 1989;143:552-555)

The increasing survival of low-birthweight neonates,[1] who are at higher risk for cerebral palsy (CP),[2,3] and the growing awareness and legislation concerning the rights of handicapped children have led to an increasing demand for physiotherapy (PT) as the primary intervention for CP. Currently, a number of different PT techniques are in vogue.[4-6] These programs are often expensive, in that they require long-term therapy, use of diverse equipment, and parental cooperation and active participation. Despite the intense commitment demanded of both the therapist and the family, arbitrary decisions may be made as to the type of PT technique to be used, and unjustified expectations might be anticipated by all those involved.

Attempts have been made to assess the efficacy of PT in CP; however, until 1973, no study employed a control group, and since then the results of studies, despite being controlled, have been inconclusive and conflicting. Concerns regarding lack of evidence for the efficacy of this intervention have been raised in the literature.[7-10] The more general employment of earlier intervention in a heterogeneous group of infants at risk (not necessarily for CP) has been reviewed using qualitative[11] and quantitative[12] methods. More specifically, the literature concerning the neurodevelopmental treatment approach for children has recently been critically reviewed using meta-analysis.[13] The latter review, however, included populations other than patients with CP and referred only to reports published up to 1982. Moreover, quantitative reviewing methods have limitations[14] that make a critical qualitative analysis of the evidence of such a limited number of investigations particularly important. The purpose of our study, therefore, was to critically review the literature published in English during the past 15 years, to evaluate the evidence supporting the value of PT in the rehabilitation of children with CP.

In assessing this problem it was necessary to consider the following two attributes: (1) efficacy: the extent to which a therapy is more useful and beneficial than useless and harmful, for the purpose for which it is advocated in ideal circumstances, and (2) effectiveness: the extent to which this efficacious intervention could be applied to all those who could benefit from it in real practice.

MATERIALS AND METHODS

A comprehensive *Index Medicus* and computer search of the literature in English dealing with evaluation of the value of PT, published between 1973 and 1987, was performed.

The six original guidelines suggested by Sackett[15] were modified by breaking them down into the following 12 criteria with which to evaluate the studies: (1) randomization of subjects to treatment groups (ie, matching of groups and allocation) after prognostic stratification; (2) study of patients representing the general spectrum of the population of patients with CP (reproducibility of exclusion and inclusion criteria); (3) description of the intervention program in sufficient detail; (4) avoidance of contamination (intervention under study applied to control subjects); (5) avoidance of cointervention (additional therapies applied to a subject of the experimental group); (6) blind assessment of outcome; (7) sufficient description of the measurements; (8) accounting for all patients (who entered the study) at its conclusion; (9) ascertainment of compliance; (10) evaluation of all relevant clinical outcomes, ie, assessment of morbidity and assessment of quality of life; (11) consideration of clinical significance; and (12) consideration of statistical significance.

To rank the studies according to their rigor of design, each criterion was assigned from 1 to 2 points if adequately fulfilled, resulting in a maximum score of 14 points.

RESULTS

The literature search yielded nine articles published between 1973 and 1988 that addressed the question of efficacy of PT for infants and children with CP[16-24] (Table 1). No study addressed the question of the effectiveness of intervention as defined above. None of the nine studies met all the criteria, and only one gained a cumulative score of 12 points (Table 2).

The number of subjects included in each study ranged from 22 to 115, and

Accepted for publication December 30, 1988.

From the Hannah Khoushy Child Development Center, Bnai Zion Medical Center (Dr Tirosh and Ms Rabino), and the Department of Pediatrics, Faculty of Medicine, Technion-Israel Institute of Technology (Dr Tirosh), Haifa, Israel.

Reprint requests to Hannah Khoushy Child Development Center, Bnai Zion Medical Center, PO Box 4940, 31048 Haifa, Israel (Dr Tirosh).

Table 1.—Description of Eight Reviewed Articles*

Study, y	Sample Characteristics	Study and Control Group Program	Evaluated Outcomes
Wright and Nicholson,[16] 1973	47 subjects up to age 6 y with spastic CP: 20 quadriplegic, 11 diplegic, 16 hemiplegic; 28 normal, 19 subnormal intelligence	16 subjects, Bobath NDT ≤12 mo, intensity unspecified; additional remediation as appropriate (including drugs); 31 subjects untreated (26 remained for a 1-y program)	Motor function, range of motion (unstandardized)
Banham,[17] 1976	16 subjects with unspecified CP and subnormal intelligence (mean ± SD IQ, 51 ± 17.5)	19 subjects, some rehabilitation and surgery; 41 subjects, rehabilitation program; nature of program unspecified	Screening only for motor development and maturity, play interest, and mental ability
Scherzer et al,[18] 1976	22 subjects, aged 5-17 mo: 11 spastic athetotic, 4 quadriplegic, 2 hemiplegic, 1 ataxic, 2 brain damaged; 6 normal intelligence, 6 educable, 6 trainable	14 subjects, Bobath NDT up to age 4 mo, conducted by parents at home, supervised semiweekly by physiotherapist; 8 subjects, passive range of motion (11 were treated for 6-12 mo; 11, >12 mo)	Motor function, neurological status, social development, home management (unstandardized)
Brandt et al,[19] 1980	34 subjects, aged 4-7 mo, mostly low birth weight, with ≥4 abnormal postural reflexes (Vojta), at risk for CP	15 subjects, Vojta technique administered by a relative supervised by a physiotherapist; 19 subjects, untreated or treated with Bobath technique as above; intensity unspecified	Neurologic status and gross motor function (technique unspecified)
D'Avignon et al,[20] 1981	30 subjects younger than 6 mo old with abnormal postural reflexes (Vojta), at risk for CP	10 subjects, Vojta technique; 12, Bobath NDT; 8, "less strictly" performed physiotherapy program; all administered by physiotherapist up to age 5 y or less if normalized (intensity unspecified)	Neurologic status, mental status (technique unspecified)
Sommerfeld et al,[21] 1981	29 subjects, aged 3-22 y, severely retarded: 5 mild, 13 moderate, 11 severe CP; 15 quadriplegic, 2 athetotic, 1 ataxic, 11 other	10 subjects, Bobath NDT treatment by physiotherapist weekly for 30 mo, additional positioning and mobilization by teacher for 5 mo; 9 subjects, same as above by teachers supervised by physiotherapist at 6-wk intervals; 10 subjects, no treatment	Neurologic status, gross motor development (unstandardized)
Kanda et al,[22] 1984	28 subjects with spastic diplegia	8 subjects, treatment ensuing before and 21 subjects after older than 6 mo of age; Vojta technique administered by parents for ≥6 mo (intensity unspecified)	Gross motor milestones: sitting, crawling, walking
Piper et al,[23] 1986	115 subjects ≤24 mo of age, birth weight 1500 g or infants at high risk for CNS dysfunction regardless of weight	56 subjects, Bobath NDT administered by parents, supervised weekly for 3 mo and biweekly for 9 mo by physiotherapist; 59 subjects, followed up with no treatment	Gross motor development, neurologic status, general psychomotor development, physical status (partly standardized instruments)
Palmer et al,[24] 1988	47 subjects, aged 9-12 mo with spastic diplegia	24 subjects, NDT for 12 mo; 23 subjects, stimulation for 6 mo—all administered by parents, supervised biweekly by physical and developmental therapists	Motor and mental quotients, neurologic status and social development quotient

*CP indicates cerebral palsy; NDT, neurodevelopmental therapy; and CNS, central nervous system.

only in three were more than 50 patients investigated (Table 3). Of the nine studies, seven[16,18-21,23,24] used random assignment, two used both study and control groups, and five included both a study and a contrast group. One study[21] used both control and contrast groups. Only one study matched subjects,[21] and three stratified them[16,23,24] (Table 3).

The subjects investigated in all of the eight studies were, by and large, representative of the population of patients with CP; however, each study differed in its inclusion criteria. For example, the study by Scherzer et al[18] included patients up to 18 months of age who suffered from different types of CP,

Table 2.—Analysis and Outcome*

Study, y	Analysis: Clinical	Analysis: Statistical	Accounted for All Patients	Positive Results	Total Score
Wright and Nicholson,[16] 1973	+	−	+	+	9
Banham,[17] 1976	−	+	+	+	4
Scherzer et al,[18] 1976	+	−	−	+	8
Brandt et al,[19] 1980	+	−	−	+	6
D'Avignon et al,[20] 1981	−	+	+	+	6
Sommerfeld et al,[21] 1981	−	+	+	−	9
Kanda et al,[22] 1984	−	+	+	+	5
Piper et al,[23] 1986	−	+	+	−	11
Palmer et al,[24] 1988	+	+	+	−	12

*Plus sign indicates presence in study; minus sign, absence from study.

Table 3.—Research Design*

Study, y	Population				Design		
	Experimental	Control	Contrast	Representative	Randomized	Matched	Stratified
Wright and Nicholson,[16] 1973	16	31	0	+	+	–	+
Banham,[17] 1976	41	0	19	–	–	–	–
Scherzer et al,[18] 1976	14	0	8	+	+	–	–
Brandt et al,[19] 1980	15	0	19	+	+	–	–
D'Avignon et al,[20] 1981	10	0	20	+	+	–	–
Sommerfeld et al,[21] 1981	10	10	9	+	+	+	–
Kanda et al,[22] 1984	8	0	21	+	–	–	–
Piper et al,[23] 1986	56	59	0	+	+	–	+
Palmer et al,[24] 1988	24	0	23	–	+	–	+

*Plus sign indicates presence in study; minus sign, absence from study.

Table 4.—Intervention and Measurements*

Study, y	Intervention			Assessment and Measurements			
	Described in Detail	No Contamination	No Cointervention	"Blind"	Described in Detail	Range of Relevant Clinical Outcomes	Compliance Ascertained
Wright and Nicholson,[16] 1973	–	+	+	+	+	–	–
Banham,[17] 1976	–	+	+	–	–	–	–
Scherzer et al,[18] 1976	–	+	+	+	+	+	–
Brandt et al,[19] 1980	–	+	+	+	–	–	–
D'Avignon et al,[20] 1981	–	+	+	–	–	–	–
Sommerfeld et al,[21] 1981	+	+	+	–	+	–	–
Kanda et al,[22] 1984	–	+	+	–	–	–	–
Piper et al,[23] 1986	+	–	+	+	+	+	+
Palmer et al,[24] 1988	+	+	+	+	+	+	+

*Plus sign indicates presence in study; minus sign, absence from study.

while Kanda et al[22] studied only children up to the age of 6 years who suffered from diplegia, and Sommerfeld et al[21] and Banham[17] studied patients with CP and mental retardation.

Only three studies[21,23,24] described the intervention characteristics in sufficient detail to enable repetition of the experiment. One study reported contamination[23] and none reported cointervention. Of the remaining studies, only one referred explicitly to these confounding factors (Table 4).

Five studies[16,18,19,23,24] reported blind evaluation of outcomes. Five studies[16,17,21,23,24] described the evaluation procedure in sufficient detail to enable replication. Seven studies[16,17,20-24] either accounted in their results for all patients who started the study or, at least, did not state otherwise (Table 2).

Ascertainment of compliance was reported only in two studies.[23,24] No study reported an attempt to assess all of the relevant outcomes, and usually only the motor and orthopedic aspects were evaluated. Three studies, however, reported the effects of the program on a wider range of outcomes, such as social maturation and home management[18,23,24] (Table 4).

Only three studies[16,18,19] evaluated clinical significance without analyzing the magnitude of its importance (eg, the extent to which the increased passive range of motion had or had not improved the child's manipulation of a table utensil) (Table 2).

Six studies[17,20-24] reported statistical significance, but only one study[24] assessed both statistical and clinical significance (Table 2). A cumulative score comprising a maximum of 14 points was used to evaluate each study. The results were as follows: Two studies[23,24] scored 11 and 12 points, respectively. Two studies[16,21] scored 9 points, one study[18] 8 points, two studies[19,20] 6 points, one study[22] 5 points, and one study[17] 4 points, out of the 14 possible points concerning design methodology and reporting criteria (Table 2).

Of these nine studies, six reported positive results regarding the efficacy of PT as a therapeutic intervention for CP. Three studies[21,23,24] found no evidence for the efficacy of this intervention. Interestingly, these three studies were among the four with the highest cumulative scores, ie, the most comprehensive research designs. These three studies considered the statistical significance of the outcomes, while the fourth article reported the clinical significance only. It failed to describe the intervention characteristics in sufficient detail (Table 2).

COMMENT

In recent years there has been a growing demand for PT in CP. The increasing number of rescued premature and low-birth-weight infants who are at high risk for CP[3] and the institution of many infant early-intervention programs account for this growing demand.

In the light of the complexity and ex-

pense of these programs, the lack of adequate evaluation of their efficacy is remarkable. The selection of a specific PT technique, however, is based on nonobjective and nonstandardized criteria and may prevent the consideration of other therapeutic approaches, thereby resulting in inferior management of the condition.

The present review revealed that over the past 15 years only nine studies have attempted to investigate the efficacy of PT for the treatment of CP. None of the studies investigated or reported its effectiveness. Despite the fact that only four studies[16,21,23,24] used a rigorous design, and three of these concluded that no evidence exists for the efficacy of the intervention, PT continues to be the most demanded treatment method for CP.

The small number of investigations and deficiency in design can be attributed to the following several factors: (1) Sample size: the high number of variables that should be controlled, due to the heterogeneity of the patient population, ie, age, type of CP, cognitive level, and other confounders, has been previously discussed.[8,10] (2) Studies addressing the outcome measures of therapeutic interventions in CP need to assess the following aspects: psychological effect, changes in social and family functioning, and developmental and physical changes. To date, all of the investigations have been deficient and require a larger sample size allowing for multivariate analysis. (3) Only a large sample of subjects with a wide age range will prevent spurious results, as a percentage of subjects will spontaneously outgrow their CP.[25] Alternatively, the use of strict inclusion criteria regarding the severity of the patient's state and/or age will reduce the risk of a type I error, ie, concluding the existence of a difference between groups when in fact it is not present. (4) It is likely that a too-narrow range of outcomes has been examined and that the instruments used to measure the changes following the intervention were not "responsive" enough. This may result in a type II error, ie, concluding that a difference between groups does not exist when in truth it does. The methodological criteria for assessing health indexes have been extensively reviewed.[26]

Physiotherapy has such an established role in primary intervention for CP that studies randomly assigning patients into a control (no intervention) or contrast (other intervention) group are considered by many to be unethical. There are no easy answers to these methodological problems. The single-subject design,[27] which occasionally has been suggested in the literature,[28,29] would certainly avoid many of the problematic issues raised in this review. However, the natural course of CP, its range of severity and type, and the many confounding variables, such as cognitive level and family functioning, cannot be properly assessed in this type of design and consequently would prevent generalization of the results. This latter approach,[30] properly employed, can be particularly useful in the investigation of innovative treatments[31,32] or as a supplement to larger experimental designs.

It is the large, collaborative, randomized, controlled trial using reliable and responsive measurements of different aspects of child and family well-being that can contribute to solving this problem. Such a study could use contrast groups and randomization procedures as suggested by Zelen[33] and thus could be reconciled with ethical considerations.

References

1. Lee K, Paneth N, Gartner LM, Pearlman MA, Gruss L. Neonatal mortality: an analysis of the recent improvement in the United States. *Am J Public Health*. 1980;70:15-21.
2. Ellenberg JH, Nelson KB. Birth weight and gestational age in children with cerebral palsy or seizure disorders. *AJDC*. 1979;133:1044-1048.
3. Stanley F. Prenatal risk factors in the study of the cerebral palsies. In: Stanley F, Alberman E, eds. *The Epidemiology of the Cerebral Palsies*. Philadelphia, Pa: JB Lippincott, 1984; 87-97.
4. Bobath B. Motor development: its effect on general development and application to the treatment of cerebral palsy. *Physiother Can*. 1971; 57:1-7.
5. Vojta V. *Die cerebralen Bewegnungsstorungen in Sauglingsalter*. Stuttgart, West Germany: Ferdinand Enke Verlag, 1976.
6. Levitt S. *Treatment of Cerebral Palsy and Motor Delay*. Philadelphia, Pa: JB Lippincott, 1977.
7. Taft L. Are we handicapping the handicapped? *Dev Med Child Neurol*. 1973;14:703.
8. Parette HP, Hourcade HJ. A review of therapeutic intervention research on gross and fine motor progress in young children with cerebral palsy. *Am J Occup Ther*. 1984;38:462-468.
9. American Academy of Pediatrics Committee on Children with Disabilities 1984-85. School-aged children with motor disabilities. *Pediatrics*. 1985;76:648-649.
10. Pless B. On doubting and certainty. *Pediatrics*. 1976;58:7-9.
11. Simeonsson RJ, Cooper D, Scheirer AP. A review and analysis of the effectiveness of early intervention programs. *Pediatrics*. 1982;69:635-641.
12. Ottenbacher K, Peterson P. The efficacy of early intervention programs for children with organic impairment: a quantitative review. *Evaluation and Progress Planning*. 1985;8:135-146.
13. Ottenbacher KJ, Biocca Z, De Cremer G, Gevelinger M, Jedlovec KB, Johnson MB. Quantitative analysis of the effectiveness of pediatric therapy: emphasis on the neurodevelopmental treatment approach. *Phys Ther*. 1986;66:1095-1101.
14. Cook TD, Leviton LC. Reviewing the literature: a comparison of traditional methods with meta-analysis. *J Pers*. 1981;48:449-461.
15. Sackett DL. How to read clinical journals, V: to distinguish useful from useless or even harmful therapy. *Can Med Assoc J*. 1981;124:1156-1162.
16. Wright T, Nicholson J. Physiotherapy for the spastic child: an evaluation. *Dev Med Child Neurol*. 1973;15:146-163.
17. Banham KM. Progress in motor development of retarded cerebral palsied infants. *Rehabil Lit*. 1976;37:13-14.
18. Scherzer AL, Mike V, Ilson J. Physical therapy as a determinant of change in the cerebral palsied infant. *Pediatrics*. 1976;58:47-52.
19. Brandt S, Lonstrup H, Marner T, Rump KJ, Selman P, Schack LK. Prevention of cerebral palsy in motor-risk infants by treatment ad modum Vojta. *Acta Paediatr Scand*. 1980;69:283-286.
20. D'Avignon MD, Noren L, Arman T. Early physiotherapy ad modum Vojta or Bobath in infants with suspected neuromotor disturbances. *Neuropediatrics*. 1981;12:232-241.
21. Sommerfeld D, Fraser BA, Hensinger RN, Beresford LV. Evaluation of physical therapy service for severely mentally impaired students with cerebral palsy. *Phys Ther*. 1981;61:338-343.
22. Kanda T, Yuge M, Yamori Y, Suzuki J, Fukase H. Early physiotherapy in the treatment of spastic diplegia. *Dev Med Child Neurol*. 1984;26:438-444.
23. Piper M, Kunos VL, Willis DM, Mazer BL, Ramsay M, Silver KM. Early physical therapy effects on the high-risk infants: a randomized controlled trial. *Pediatrics*. 1986;78:216-224.
24. Palmer BP, Shapiro BK, Wachtel RC. The effects of physical therapy on cerebral palsy. *N Engl J Med*. 1988;318:803-808.
25. Nelson KB, Ellenberg JH. Children who outgrew cerebral palsy. *Pediatrics*. 1982;69: 529-536.
26. Kirshner B, Guyatt G. A methodological framework for assessing health indices. *J Chronic Dis*. 1985;38:7-36.
27. Louis TA, Lavori PW, Bailar JC, Polansky M. Crossover and self-controlled designs in clinical research. *N Engl J Med*. 1984;310:24-31.
28. Gonella C. Designs for clinical research. *Phys Ther*. 1973;53:1276-1283.
29. Martin JE, Epstein LH. Evaluating treatment effectiveness in cerebral palsy. *Phys Ther*. 1976;56:285-294.
30. Harris SR, Ridfle K. Effects of inhibitive ankle-foot orthoses on standing balance in a child with cerebral palsy: single-subject design. *Phys Ther*. 1986;66:663-667.
31. Laskan CA, Mullen SL, Nelson DL, Willson-Broylen M. Enhancement of two motor functions of the lower extremity in a child with spastic quadriplegia. *Phys Ther*. 1985;65:11-16.
32. Hinderer KA, Harris SR, Purdy AH, et al. Effects of tone-reducing vs standard plaster casts on gait improvement of children with cerebral palsy. *Dev Med Child Neurol*. 1988;30:370-377.
33. Zelen M. A new design for randomized clinical trials. *N Engl J Med*. 1959;300:1242-1245.

Unintentional Injuries

Risk Factors in Preschool Children

Claire C. Bourguet, PhD, Robert E. McArtor, MD, MPH

• **Successful strategies for preventing childhood injuries require better understanding of injury epidemiology. A case-control study was designed to identify risk factors for injury among preschool patients of a university-affiliated, community-based family practice center. Thirty-four children who were injured during a 1-year period and 36 age- and sex-matched controls were included. A description of the injury incident and data from each child's medical record and a parent interview were recorded. All injuries were relatively minor. The following were associated with increased injury risk: a history of a chronic medical condition; weight in the lowest 25th percentile of the national distribution; birth order of third or later in the family; maternal education higher than the high school level; and, possibly, a history of previous injury.**

(*AJDC*. 1989;143:556-559)

Injuries cause 46% of deaths among children aged 1 to 4 years, and 55% of deaths among children aged 5 to 14 years, in the United States.[1] The 1980-1981 National Health Survey indicates that each year, 35% of children under age 6 years sustain an injury severe enough to cause them to seek medical care or to restrict activity for a day.[2]

Patterns of children's injuries differ from adult patterns. Children suffer higher mortality from pedestrian accidents, fires and burns, drowning, and aspiration and suffocation. Preschool children have the highest mortality from these causes,[1] and are also at excess risk of nonfatal falls.[3,4] They are more likely to be injured at home and are more likely to be treated at a hospital emergency department (ED) than persons in other age groups.[2,3]

The 1990 Health Objectives for the Nation[5] emphasize injury prevention. Understanding the epidemiology of injuries in specific age groups is essential for developing prevention strategies. The study reported here was designed to identify characteristics of preschool children and their families that place the children at increased risk of injury.

PATIENTS AND METHODS

Injured children were identified between May 1, 1986, and April 30, 1987, at the Family Practice Centers of the Aultman Hospital in Canton, Ohio. This family practice program serves a low- to middle-income, white population. The study was restricted to children younger than 6 years of age.

A matched case-control study design was used. The injured children (case patients) were seen either at a family practice center or at the ED. Children seen at the ED were identified by ED reports, which are filed in the medical record. The study included injuries that were severe enough to result in an office or ED visit or hospitalization. Injured children were recruited into the study as the injuries occurred, usually within 2 weeks of the event. One case of suspected child abuse was excluded.

At the time each case patient was identified, an uninjured child (control subject) of the same sex and age (within 1 year) was chosen. Control subjects were chosen by locating the first eligible child sequentially in the medical records starting at the case patient's record. Control subjects were required to have had at least one office visit during the year prior to the injury of the case patient.

Data were collected from three sources. First, a record of the nature and circumstances of the injury was completed by the physician or abstracted from the ED report. The injury site and severity were coded using the "trauma chart" developed by Greenspan and colleagues.[6]

Second, a questionnaire was completed by the child's parents. This questionnaire collected demographic, socioeconomic, and family health data. Demographic data included age, sex, and relationship to the index child of all household members (used to calculate birth order); number of rooms in house (used to calculate a crowding index); and parents' religion, age, and marital status. Socioeconomic data included annual family income and parents' education, employment status, and occupation and industry. Family health data included any chronic physical or mental health condition of any household member, including drug or alcohol abuse. The questionnaire was mailed to the parents, and nonrespondents were interviewed by telephone.

Third, the child's medical record was abstracted at a family practice center. Data included standardized height and weight, developmental measures, congenital defects, chronic conditions, allergies, behavior problems, and previous injuries. A chronic condition had to have been active for more than a year. Allergies and behavior problems required referral to a specialist. For case patients and their matched control subjects, data were abstracted up to the case patient's injury date.

The Institutional Review Boards of the Northeastern Ohio Universities College of Medicine and the Aultman Hospital approved the study. A parent of each child who participated in the study gave informed consent.

The control subjects were selected using an incidence density sampling strategy. This strategy allows estimation of the ratio of the rate of injury in the presence of a risk factor to the rate of injury in the absence of the risk factor (rate ratio [RR]). Under incidence density sampling, a control subject is identified for each case patient when the case patient is identified. If the control subject later develops the disease under study, that individual remains in the control group and is also included as a case patient.[7,8] The analogy may be made to the calculation of a disease rate, in which an individual contributes to the denominator of the rate while disease free and contributes to the numerator of the rate if disease develops.

Case patients and control subjects were matched for age and sex, since these factors are strongly associated with injury risk. It was expected that the matched design would contribute statistical efficiency beyond that obtainable from a random sample of control subjects.

The data analyses were carried out in two phases: first, the crude association (adjusted for age and sex) of each variable with injury was estimated; second, for variables that showed an initial association, the RR for injury adjusting for potential confounding variables was estimated using a conditional linear logistic model for matched data.

Four separate full logistic models were specified, one for each of the following categories: child's medical history; demographic factors; socioeconomic factors; and family

Accepted for publication November 21, 1988.

From the Division of Community Health Sciences (Dr Bourguet) and the Department of Family Medicine (Dr McArtor), Northeastern Ohio Universities College of Medicine, Rootstown, and the Aultman Hospital Family Practice Center, Canton, Ohio (Dr McArtor).

Reprint requests to the Division of Community Health Sciences, Northeastern Ohio Universities College of Medicine, PO Box 95, Rootstown, OH 44272 (Dr Bourguet).

health factors. Because of the limited sample size, it was difficult to combine these models further. Consequently, although adjustment has been made for confounding within each category, confounding may still exist between variables in different categories.

To obtain RR estimates that were both valid and precise, the following strategy was used to develop the final logistic model.[9] Starting from a model that incorporated all variables of a category, each model was simplified by sequentially removing variables. Variables were removed if they were unrelated to the outcome (criteria of statistical significance) and if their removal did not appreciably change the regression coefficients of the remaining variables. This procedure was continued until the precision of the fit of the model could not be further improved without sacrificing validity, ie, appreciably altering the regression coefficients.

Adjusted RRs and 95% confidence intervals (CIs) are shown for variables that were included in the best-fitting models. The width of the CI gives an indication of the adequacy of the sample size for the analysis. Wide CIs indicate imprecise estimates, which can result from small sample size. For variables that were not included in the final logistic model, only the crude RRs are shown. For variables that are measured on a ratio scale, the RRs were calculated using the mean value of the study members who were classified in that group, unless noted otherwise.

RESULTS

During the study year, 43 children presented to one of the study sites with an injury. Fifteen children were brought to a family practice center and 28 children were brought to the ED. Four children who were chosen as control subjects early in the study later became case patients. Two of these children are included in the study in both their case patient and control subject status, as is required by the sampling strategy.[7,8] Parents of the other 2 children either could not be contacted or refused to participate. In one family, a brother was chosen as a control subject and his sister was included later when she became a case patient. No other study members were related.

The parents of 59 uninjured children were contacted to enroll their children as control subjects. The final sample consisted of 34 injured children and 36 matched control subjects. The two additional control subjects resulted from matched pairs in which the parents of the control subject agreed to participate in the study but the case patient's did not. As these two control subjects met the age and sex matching criteria for other case patients in the study, they were reassigned to those case patients. The overall participation rate was higher for the case patients (79%) than for the control subjects (61%). Approximately the same proportions (21% and 29%) responded initially by mail. The participation rate was higher for case patients identified at a family practice center (87%) than at the ED (75%).

Among the participating case patients there were 23 external injuries (68%), 15 (44%) of which were to the face or scalp. There were 5 (15%) head injuries, 4 (12%) injuries to the extremities or bony pelvis, 1 injury (3%) to the spine, and 1 (3%) poisoning. Twenty-nine injuries (88%) were classified as minor and 4 (12%) as moderate. These distributions are similar to those of the total group of injured children, including nonparticipants.

Table 1 shows the cause of injury for all injuries and for the study participants. Injuries were primarily caused by falls or impact with household furnishings or structures. Those involving toys most often involved bicycles. One injury caused by "other persons" was caused unintentionally by a parent, and the remainder by other children.

Table 2 shows the distribution of physical and clinical characteristics of the children and their relationship to injury. Two thirds of the case patients were males and the modal age is 1 year. In the best-fitting logistic model, both weight in the lowest quartile and presence of a chronic condition were independently associated with injuries. Low weight increased a child's risk of injury by a factor of 4.9, and a chronic condition increased the risk by a factor of 7.2. Neither height, low birth weight, nor premature birth was an independent predictor of injury. A history of previous injuries increased the rate 5.2 times, but this relationship was not statistically significant. Allergies, behavior problems, and developmental abnormalities were rare and are not shown.

Demographic, socioeconomic, and family health factors were examined in three separate analyses. Among demographic factors, only birth order and maternal age were associated with injuries. Children born third or later in the family were at 5.7 times (95% CI, 1.02 to 31.36) increased risk. There was a statistically nonsignificant dose-response relationship of increasing injury rates with decreasing maternal age. In contrast to children with mothers aged 30 years or older, mothers aged 25 to 29 years had an RR of 1.8 (CI, 0.8 to 3.8), and mothers aged less than 25 years had an RR of 2.5 (CI, 0.7 to 8.6). Among socioeconomic factors, there was a curvilinear association of maternal education with injury risk. Children with mothers who were only high school graduates had the lowest risk. Children whose mothers had less than a high school education were at somewhat increased risk (RR = 2.5; CI, 0.5 to 12.4). Children whose mothers had attended college were at greatly increased risk (RR = 9.7; CI, 1.1 to 89.2). This was not due to the mother's occupational level, since children of mothers with professional occupations were at the lowest risk. Health status of family members was not associated with injury risk.

Table 1.—Cause of Injury Among All Reported Injuries and Study Participants

Cause	All Injuries, No. (%) (n = 43)	Participants, No. (%) (n = 34)
Motor vehicle (passenger)	2 (5)	2 (6)
Motor vehicle (pedestrian)	2 (5)	1 (3)
Toy	5 (12)	4 (12)
Bicycle	3 (7)	3 (9)
Fall	12 (28)	9 (26)
Household object	13 (30)	12 (35)
Poison	1 (2)	1 (3)
Other person	4 (9)	3 (9)
Dog bite	1 (2)	0
Unknown	3 (7)	2 (6)

COMMENT

These data concur with previous reports that injuries in preschool children primarily occur at home and are caused by falls or by impact with household structures or furniture.[3,4,10,11]

Because of the small number of children in the study, there was inadequate statistical power to confirm or refute many associations that have been previously reported. For this reason, we fo-

Table 2.—Distribution of Physical and Clinical Characteristics of Injured Patients and Control Children and Rate Ratios (RRs) for Injury

	Cases/Controls, No.	Crude* RR	Adjusted† RR	95% Confidence Interval
Sex				
M	23/25	...	...	
F	11/11	...	...	
Age, y				
<1	2/4	...	...	
1	10/6	...	...	
2	4/8	...	...	
3	8/5	...	...	
4	8/6	...	...	
5	2/7	...	...	
Race				
Nonwhite	3/1	3.7	...	
White	31/35	1.0	...	
Birthweight				
<3000 g	14/8	1.9	1.8	0.5-6.8
≥3000 g	20/28	1.0	1.0	
Gestation				
≤37 wk	5/2	3.5	...	
≥38 wk	29/34	1.0	...	
Percentile of height‡				
≤25	13/13	1.1	0.4	0.1-1.4
≥26	21/23	1.0	1.0	
Percentile of weight‡				
≤25	14/6	2.8	4.9	1.0-25.2
≥26	20/30	1.0	1.0	
Chronic conditions, No.				
≥1	10/5	2.7	7.2	1.2-42.2
0	24/31	1.0	1.0	
Congenital defects, No.				
≥1	5/8	1.1	...	
0	29/28	1.0	...	
Previous Injuries, No.‡				
≥1	13/10	2.2	5.2	0.8-36.0
0	21/26	1.0	1.0	

*RRs are adjusted for age and sex.
†Adjusted RRs are shown only for variables included in best-fitting model.
‡These entries are coded as binary variables.

cus the discussion on the associations that were seen in the data, especially those that represent new or controversial findings.

The presence of a chronic health condition increased the probability of injury by a factor of 7.2. Previous reports examining the possible association between a child's medical history and injury risk have been inconsistent.[12-16] These inconsistencies may result from the diversity of conditions that have been included or from failure to control other confounding factors. Chronic conditions identified in this study included enuresis, otitis media, hydrocele, exotropia, alternating esotropia, phimosis, failure to thrive, eczematous dermatitis, asthmatic bronchitis, and chronic vomiting.

Horowitz and colleagues[14] described children who were members of a prepaid health plan. They found no association of injuries with the "child's baseline health score," but noted an odds ratio of 2.22 for children with high levels of concurrent utilization of the health plan after controlling for the former factor. This finding suggests that the association of injury with chronic conditions seen in our data may be confounded by a tendency to utilize medical services. We cannot address this issue since we did not collect utilization data.

Children in the lowest quartile of the standardized weight distribution were 4.9 times as likely to be injured according to this study. This association was independent of the child's height and of chronic conditions, but is of marginal statistical significance. Analogous to chronic conditions, this association might be confounded by a tendency to utilize medical service. Although several studies have examined the height and weight distributions of study members, an association of low weight with injury risk has not been previously reported.[13,15,17] Wilmore and Pruitt[18] report, however, that children admitted for burns to the US Army Institute of Surgical Research were overweight relative to the norms for their ages.

The concept of the "accident-prone child" is controversial in the pediatric literature.[19,20] Results of studies of injury risk among children who have previously sustained injuries are contradictory.[12,14,16,21,22] In the current study, children who had a previous injury recorded in their charts were at 5.2 times increased risk of sustaining an injury, although this finding may result from chance.

Manheimer et al[21] suggested that the relationship between previous injuries and injury risk resulted from an increased tendency of parents to seek medical care for children with minor injuries. However, in their data, the proportion of minor injuries increased only slightly as the number of previous injuries increased.

In our study, children born third or later in the family were at increased risk, independent of family size. Libber and Stayton[15] reported that among children hospitalized for burns, there was an increased likelihood of the child being a younger sibling in the family. This may be because the average age of burn victims is relatively young. In contrast, Manheimer et al[21] found that children who had no older sibling were at increased risk of injury, and Horowitz et al[14] found no association with birth order.

Beyond risk factors associated directly with the child, only maternal factors showed an association with injury risk. There was a consistent but statistically nonsignificant relationship between increasing injury risk and decreasing maternal age. Beautrais and colleagues[23,24] found a similar relationship for medically treated poisonings but not for all poisonings or all injuries. Other authors report no association between injury and maternal age.[12,14]

There was a curvilinear relationship with maternal education. Children whose mothers had attended college were at highest risk. Beautrais and colleagues[24] found an inverse relationship with maternal education. Other authors report no association of maternal education with injury risk.[12-14]

Interpretation of these results requires awareness of the limitations of the data and methods. Because of the small sample size, the reported confidence intervals may be wide and the lower bounds are close to 1.0. The CIs were calculated without adjusting the level of α error for multiple comparisons. For these reasons, and for the reasons relating to potential sources of bias (discussed below), the reported results should be viewed as preliminary.

Several potential sources of bias must be considered. Data collection was not blind, leading to the possibility of observer bias. Interview forms were standardized and coding rules were specified in advance to avoid this bias.

The response rate among control subjects was lower (61%) than among case patients (79%). This was due to a larger proportion of control subjects than case patients who had moved or had no telephone or a disconnected telephone (17% vs 9%), and a larger proportion who had working telephones but could not be contacted (12% vs 5%). These differences may reflect recency of medical care contact, since case patients had been seen at injury but control subjects had been seen only within the previous year.

Alternatively, the potential for selection bias exists. Selection bias in a case-control study may occur if factors related to the risk factor status of the study members influence the probability of selection into the study differently for case patients than control subjects.[8] The direction of the bias depends on the risk factor involved. For example, if participation by control subjects were increased by a factor such as chronic illness, the control subjects would be more similar to the case patients, resulting in a conservative bias. Since information about the nonparticipants is lacking, this must remain speculative.

Injured children were identified only at the two family practice centers and the affiliated hospital ED. It is possible that some injured children were not identified because they were treated at another hospital or at an urgent care center. These true case patients could potentially be included in the control group. Such misclassification would generally result in a conservative bias, since it would make the distribution of risk factors in the control group more similar to that of the case patients. However, if the use of alternative sources of medical care were differentially associated with a risk factor, the possibility of bias away from the null exists. The parents' questionnaire did inquire about physician visits and hospitalizations within a 3-month period. Parents of case patients often volunteered the injury incident in response, while parents of control subjects mentioned only illness visits.

All injuries were relatively minor, and the data may not be generalizable to children with more severe injuries. Similarly, the definition of a case patient required that parents judge the injury to be severe enough to require medical care. Other limitations to the generalizability of the findings result from the characteristics of the source population. The children were of preschool age, mostly white, and from urban and suburban residences. Sixty-three percent came from families with annual incomes of less then $20 000.

Injuries are an unusual health problem because the most effective solutions are based historically on structural or regulatory changes, for example, childproof packaging or seatbelt legislation. Studies that identify personal characteristics of high-risk individuals can be criticized for not suggesting obvious methods of intervention. Such studies can also be used unproductively to blame the victim. This is a special problem for studies of "injury-prone" children, which may imply a personality characteristic while ignoring environmental explanations. However, the medical and public health communities are searching for new injury prevention strategies. Studies of high-risk individuals may contribute to these strategies.

This study was supported by a grant from the United Way of Stark County, Ohio.

The authors express their appreciation to Brenda Papincek, MA, for data collection; to the staff of the Aultman Hospital Family Practice Centers for identifying study members; and to Cyndi Dubbert for manuscript preparation.

References

1. Baker SP, O'Neill B, Karpf RS. *The Injury Fact Book*. Lexington, Mass: Lexington Books; 1984.
2. Collins JG. *Persons Injured and Disability Days Due to Injuries: United States, 1980-81*. Washington, DC: National Center for Health Statistics; 1985. Vital and Health Statistics, series 10, No. 149, US Dept of Health and Human Services publication PHS 85-1577.
3. Fife D, Barancik JI, Chatterjee BF. Northeastern Ohio trauma study: II. injury rates by age, sex, and cause. *Am J Public Health*. 1984;74:473-478.
4. Garrettson LK, Gallagher SS. Falls in children and youth. *Pediatr Clin North Am*. 1985;32:153-162.
5. Office of Disease Prevention and Health Promotion. *The 1990 Health Objectives for the Nation: A Midcourse Review*. Washington, DC: US Dept of Health and Human Services; 1986.
6. Greenspan L, McLellan BA, Greig H. Abbreviated injury scale and injury severity score: a scoring chart. *J Trauma*. 1985;25:60-64.
7. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol*. 1982;116:547-553.
8. Kelsey JL, Thompson WD, Evans AS. *Methods in Observational Epidemiology*. New York, NY: Oxford University Press Inc; 1986.
9. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Methods*. Belmont, Calif: Lifetime Learning Publications; 1982.
10. Gallagher SS, Finison K, Guyer B, Goodenough S. The incidence of injuries among 87 000 Massachusetts children and adolescents: results of the 1980-81 statewide childhood injury prevention program surveillance system. *Am J Public Health*. 1984;74:1340-1347.
11. Rivara FP. Childhood injuries: III. epidemiology of non–motor vehicle head trauma. *Dev Med Child Neurol*. 1984;26:81-87.
12. Shaw MTM. Accidental poisoning in children: a psychosocial study. *NZ Med J*. 1977;85:269-272.
13. Langley J, Silva PA, Williams S. A study of the relationship of ninety background, developmental, behavioral and medical factors to childhood accidents. *Aust Paediatr J*. 1980;16:244-247.
14. Horowitz SM, Morgenstern H, DiPietro L, Morrison CL. Determinants of pediatric injuries. *AJDC*. 1988;142:605-611.
15. Libber SM, Stayton DJ. Childhood burns reconsidered: the child, the family, and the burn injury. *J Trauma*. 1984;24:245-252.
16. Schor EL. Unintentional injuries: patterns within families. *AJDC*. 1987;141:1280-1284.
17. Meyer RJ, Roelofs HA, Bluestone J, Redmond S. Accidental injury to the preschool child. *J Pediatr*. 1963;63:95-105.
18. Wilmore DW, Pruitt BA. Fat boys get burned. *Lancet*. 1972;2:631-632.
19. Jones JG. The child accident repeater. *Clin Pediatr*. 1980;19:284-288.
20. Langley J. The 'accident prone' child: the perpetration of a myth. *Aust Paediatr J*. 1982;18:243-246.
21. Manheimer DI, Dewey J, Mellinger GD, Corsa L. Fifty thousand child-years of accidental injuries. *Public Health Rep*. 1966;81:519-533.
22. Manheimer DI, Mellinger GD. Personality characteristics of the child accident repeater. *Child Dev*. 1967;38:491-513.
23. Beautrais AL, Fergusson DM, Shannon FT. Accidental poisoning in the first three years of life. *Aust Paediatr J*. 1981;17:104-109.
24. Beautrais AL, Fergusson DM, Shannon FT. Childhood accidents in a New Zealand birth cohort. *Aust Paediatr J*. 1982;18:238-242.

Sports Medicine

William B. Strong, MD, Augusta, Ga
Carl L. Stanitski, Pittsburgh, Pa
Ronald E. Smith, PhD, Seattle, Wash
Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*As more children become involved in organized sports there is an increasing concern as to how these young athletes will be divided for competitive appropriateness. Both age and weight classifications have been routinely used. However, the smaller, older, more mature boy has been noted to have a distinct advantage in competition when compared with the less mature boy of similar age and weight. The data in the present study clearly demonstrate the greater strength characteristics that are measurable in more mature adolescents and suggest the need for more equitable classification of young athletes.*—W.B.S.

Strength, Flexibility, and Maturity in Adolescent Athletes

Michael Pratt, MD, MS

• The relationship between lower-extremity strength and flexibility and maturational status as measured by Tanner staging (TS) was assessed in 84 male high school athletes. The sum of one-repetition maximum lifts for knee extension and flexion was determined and flexibility was measured with the American Alliance of Health, Physical Education, Recreation, and Dance sit-and-reach test. Chronologic age, body weight, and percent fat were also recorded. Strength and flexibility were compared for each maturational and chronologic age category. Maturational age was better correlated with strength and flexibility than was chronologic age. All correlations were significant. Multiple regression analysis demonstrated significant correlations of TS and age with strength and flexibility. Tanner staging had greater predictive value than age for strength and flexibility. After adjusting for age, the relationship between TS and strength remained significant.

(*AJDC* 1989;143:560-563)

Accepted for publication Nov 4, 1988.

From the Division of Sports Medicine, Departments of Orthopaedics and Pediatrics, University of Washington School of Medicine, Seattle. Dr Pratt is now with the National Institutes of Health, Bethesda, Md.

Reprint requests to National Heart, Lung, and Blood Institute, National Institutes of Health, Administrative Office, DECA Federal Building/Room 204, 7550 Wisconsin Ave, Bethesda, MD 20892 (Dr Pratt).

The past two decades have seen a marked change in organized sports competition for children. More than one half of the boys and one third of the girls in the United States who are between the ages of 8 and 16 years are now involved in organized athletic competition.[1] At least 5½ million young Americans participate in high school athletics.[2] The rapid increase in youth sports participation has been accompanied by parallel changes in childhood patterns of free play and parental roles in youth sports. Concern has arisen over a potential epidemic of overuse injuries that might result as children substitute the stereotypical demands of single-sport activity for the diversity of free play.[3] It has been suggested that adolescents are particularly vulnerable to overuse injuries during periods of rapid growth, perhaps in part because of imbalances in muscle strength and flexibility.[3]

The risk of competitive mismatching also peaks during early adolescence, when individuals of identical chronologic age may differ by as much as five years in maturational age.[4] The failure of most parents, coaches, physicians, and adolescent athletes to consider developmental variation often leads to inappropriate performance expectations and an unsatisfactory sports experience for all.[5]

Unfortunately, clear guidelines for determining sports participation or restriction on an equitable and safe basis have yet to be formulated. Traditionally, age and grade level have been the sole determinants of competitive level. Increased awareness of the impact of physical maturation on sports performance has led to consideration of maturity status, often assessed by Tanner staging (TS).[6] Hafner and colleagues[7] developed an experimental program in New York state junior and senior high schools in which TS, sports skills and experience, and fitness were considered in addition to age and grade level in determining eligibility for interscholastic sports. They reported that their program placed athletes at appropriate competitive levels and that injury rates were low compared with previous reports.[2] Kreipe and Gewanter[8] evaluated physician-assessed and self-assessed TS and grip strength and developed screening criteria for sports participation based on their interrelationships. They noted that immature boys (TS II and III)

Table 1.—Body Composition, Strength, and Flexibility Data by Tanner Stage Group*

Tanner Stage	No. of Subjects	Age, y	Weight, kg	% Fat	LBW	Strength	SPB	SPL	Flexibility, cm
II	12	14.9±0.6	58.1±10.6	10.2±7.2	113.7±14.9	99.1±27.3	1.72±0.40	1.92±0.43	22.6±8.4
III	30	15.1±0.7	61.6±8.7	7.9±4.1	124.4±14.1	115.5±34.5	1.87±0.46	2.04±0.51	24.6±8.7
IV	29	16.1±0.9	72.1±9.6	10.0±5.1	141.9±12.7	146.8±37.3	2.04±0.45	2.27±0.49	29.4±9.2
V	13	16.9±0.7	79.3±13.1	11.8±4.4	153.1±20.4	160.0±31.4	2.04±0.35	2.31±0.36	35.2±9.6
Total	**84**	15.7±1.1	67.5±12.3	9.6±5.1	133.4±19.6	130.9±39.5	1.93±0.44	2.14±0.49	27.6±9.7

*Data are the mean±SD. Flexibility is represented by the sit-and-reach score and strength by the total weight lifted in kilograms. LBW indicates lean body weight; SPB, strength per body weight; and SPL, strength per lean body weight.

Table 2.—Body Composition, Strength, and Flexibility Data by Age Group*

Age, y (Mean)	No. of Subjects	Tanner Stage	Weight, kg	% Fat	LBW	Strength	SPB	SPL	Flexibility, cm
13.0-13.9 (13.7)	3	2.7	61.2±9.5	8.4±3.1	123.2±18.4	98.6±27.7	1.59±0.28	1.75±0.36	26.3±8.7
14.0-14.9 (14.6)	25	3.0	61.6±10.9	9.2±5.7	122.3±17.8	112.7±39.1	1.82±0.47	2.01±0.52	25.2±8.0
15.0-15.9 (15.5)	23	3.2	64.0±8.8	8.2±3.4	128.9±16.0	125.9±37.7	1.97±0.49	2.15±0.54	25.1±8.1
16.0-16.9 (16.4)	20	4.0	75.1±13.8	11.1±6.8	145.1±16.3	151.4±30.9	2.03±0.37	2.29±0.39	29.6±12.6
17.0-17.9 (17.4)	13	4.6	74.6±9.8	10.5±3.4	146.7±18.2	150.0±38.2	2.00±0.39	2.24±0.42	34.1±7.9
Total	**84**	3.5	67.5±12.3	9.6±5.1	133.4±19.6	130.9±39.5	1.93±0.44	2.14±0.49	27.6±9.7

*Data are the mean±SD. Flexibility is represented by the sit-and-reach score and strength by the total weight lifted in kilograms. LBW indicates lean body weight; SPB, strength per body weight; and SPL, strength per lean body weight.

could be differentiated from mature boys (TS IV and V) by grip strength, with a sensitivity of 87% and a specificity of 91%. They concluded that measures of strength and maturity status were useful for determining athletic eligibility.

The present study was designed to extend the data on maturity status, strength, and flexibility to the lower-extremity and to assess the relative predictive values of chronologic age and TS for lower-extremity strength and flexibility. The hypothesis was that TS would correlate more strongly with indexes of lower-extremity strength and flexibility than would chronologic age. It was also hypothesized that relative deficits in strength and flexibility would be observed during TS III, the rapid-growth phase. Linear growth occurs initially in the bones of the extremities and spine.[9] Muscle and tendon growth lag behind, creating a temporary disparity between bone and muscle-tendon length during TS III. Micheli[3] proposed that this disparity results in a loss of strength and flexibility during the rapid-growth spurt that may predispose adolescents to overuse injuries.

SUBJECTS AND METHODS

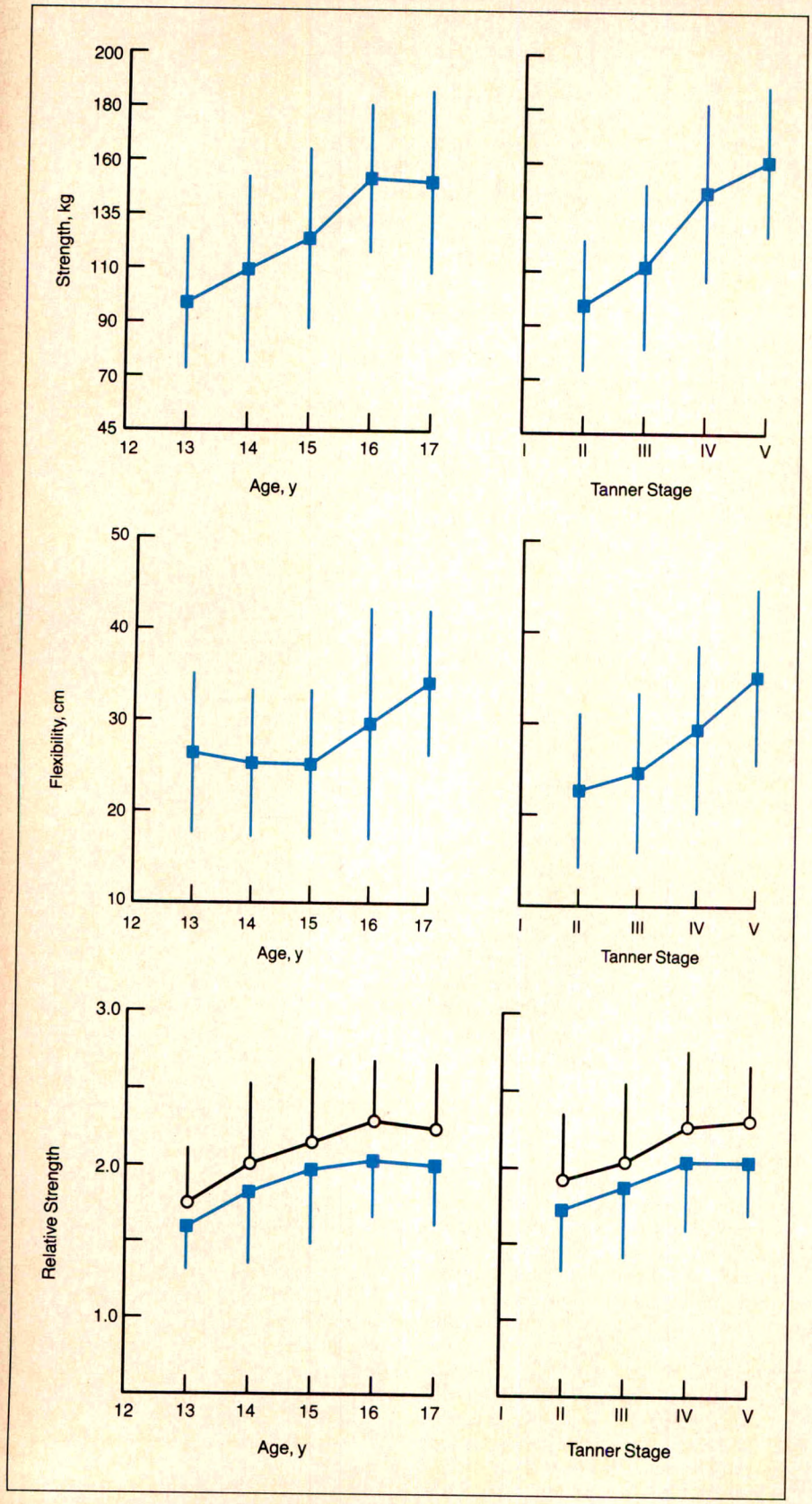
Lower-extremity strength and flexibility, body composition, and maturity status were determined for 84 male students at a private high school in Seattle between August 1984 and February 1985. Fifty-five of the subjects were evaluated during group preparticipation physical examinations for interscholastic football, cross country, golf, basketball, and wrestling. An additional 29 subjects were drawn from physical education classes at the same high school. All subjects and their parents or guardians read and signed an institutionally approved informed consent form before the evaluations.

Sexual maturity was determined by assessment of pubic hair growth and pattern with Tanner's criteria.[6] Tanner's stage ratings of I to V were assigned to each subject by an examining physician. Body weight in pounds was measured on a calibrated scale, and percent body fat was estimated after skin-fold measurements. One investigator experienced in skin-fold caliper use performed all tests with a calibrated Harpenden skin-fold caliper. Pectoral and abdominal skin folds, as well as those of the anterior aspect of the thigh, were used to produce an estimate of body composition following the age-specific protocol described by Pollock and associates.[10] This equation has been validated for use in adolescent male athletes.[11]

Lower-extremity flexibility was assessed with the American Alliance of Health, Physical Education, Recreation, and Dance sit-and-reach test for hamstring and low back flexibility.[12] Scores were recorded as the distance in centimeters that could be reached by the extended fingers with the end of the toes set at 23 cm. Lower-extremity strength was evaluated by double leg-knee extension and knee flexion exercises performed on a leg bench. One-repetition maximum lifts for knee extension and knee flexion were determined with a series of three or four trials of progressively greater weight. The maximum weights lifted for knee extension and flexion were summed to produce a single value representative of overall lower-extremity strength. Strength relative to size and lean body mass was expressed by dividing the absolute strength in kilograms by total body weight (SPB) and by lean body weight (SPL). These values provided a measure of the ability of a given muscle mass to produce force at each developmental stage. All lifts were performed under the supervision of a school athletic trainer. Maturity status and the measures of strength and flexibility were assessed independently by separate investigators.

RESULTS

The mean age of the 84 male subjects was 15.7 years (range, 13.6 to 17.8



Lower-extremity strength (top), flexibility (middle), and strength per lean body weight (circles) and strength per body weight (squares) (bottom) plotted against chronologic age in years and developmental status (Tanner stage).

years). The mean TS was 3.5, with stages II through V represented. Body weight ranged from 44.5 kg to 106.8 kg, with a mean of 67.5 kg. Mean percent body fat was 9.6% (range, 2.9% to 32.0%). Total leg strength ranged from 63.6 kg to 243.2 kg with a mean of 130.9 kg. Sit-and-reach flexibility ranged from 7.0 cm to 50.0 cm, with a mean of 27.6 cm. Subjects were grouped by TS and by chronologic age, and the group means and SDs for each variable were calculated. These data are summarized in Tables 1 and 2.

Absolute strength and flexibility increased progressively from TS II through TS V (Table 1). Strength relative to total body weight and lean body mass increased from TS II to TS IV, but no further increase was noted for TS V. When the subjects were grouped by age, a similar pattern of strength increases from ages 13 through 16 years and a plateau at age 17 years was noted (Table 2). Flexibility was relatively constant between ages 13 and 15 years but increased substantially by ages 16 and 17 years (Table 2). Strength and flexibility tended to increase with both age and TS and the rates of increase showed marked acceleration, followed by a plateau between ages 15 and 16 years and TS III and TS IV (Figure).

Statistical analysis was performed to assess the validity of the observed trends in our data and the relative predictive values of TS and chronologic age for lower-extremity strength and flexibility. Multiple simple Pearson correlations indicated that TS was significantly correlated ($P<.05$) with strength ($r=.527$), SPB ($r=.246$), SPL ($r=.287$), flexibility ($r=.416$), and body weight ($r=.587$). Age was also significantly correlated ($P<.05$) with strength ($r=.417$), SPB ($r=.202$), SPL ($r=.235$), flexibility ($r=.322$), and body weight ($r=.453$). For all variables measured, TS was a better predictor than age.

When assessed by multiple regression analysis, TS and age were also significantly correlated ($P<.05$) with strength ($r=.534$) and with flexibility ($r=.420$). The relative contributions of TS and of age to these positive correlations was assessed by converting the regression coefficients into β weights. Analysis of β weights showed that for

both strength (.447 vs .119) and flexibility (.362 vs .081), TS had a stronger predictive value than did age. Tanner stage and age had weak ($r = .293$) but significant ($P < .05$) correlations with SPL. Again, TS ($\beta = .235$) had greater predictive value than did age ($\beta = .078$). No correlation of TS and age with SPB was noted.

Additional analysis of the data was performed to determine whether TS retained significant predictive value after adjusting for age-associated increases in strength and flexibility. Strength, flexibility, SPB, and SPL were assessed by analysis of covariance with TS as the primary variable and age as the covariate. After adjusting for age, strength was significantly ($P < .05$) related to TS, and the relationship between TS and flexibility approached significance. Total body weight and SPL were not significantly related to TS after adjustment for age.

COMMENT

Analysis of our data by simple correlations, multiple regression, and analysis of covariance demonstrated that TS is better correlated with all measures of strength and flexibility than is chronologic age. Much of the predictive value of TS may lie in its close association with body weight and lean body mass, which are in turn highly correlated with increased strength.[13,14]

Previous investigators have proposed that relative deficits in strength and flexibility during the period of maximal linear growth (TS III) may account for higher rates of overuse injuries in adolescent athletes.[3] No evidence of such deficits was apparent in our cross-sectional sample. However, we observed a clear break in the TS strength and TS flexibility curves between TS III and TS IV. This finding mirrors that of Kreipe and Gewanter,[8] who noted that immature (TS II and III) and mature (TS IV and V) boys could be accurately differentiated by grip strength alone. Longitudinal investigations by Tanner and Davies,[6,13] Stolz and Stolz,[14] and Carron and Bailey[15] have delineated the normal pattern of growth. Maximal linear growth (peak height velocity) takes place during TS III. Peak weight-gain velocity follows zero to six months later and maximal strength gains are not realized for an additional six to 12 months. Implicit in this sequence is the hypothesis that strength depends on a qualitative developmental process as well as an increase in muscle mass. When expressed as a ratio of strength to lean body weight (SPL), our data are consistent with this hypothesis. Subjects at TS II and TS III had a mean SPL of 2.01, compared with 2.28 for subjects at TS IV and TS V. Our assessment of maturity status and lower-extremity strength and flexibility in 84 adolescent males demonstrated that variability in size, strength, and flexibility was more highly correlated with maturity status as measured by TS than with chronologic age. Boys at TS II and TS III tend to be markedly smaller, weaker, and less flexible than boys at TS IV and TS V.

This work was done in the Division of Sports Medicine of the University of Washington, Seattle, at the invitation of Nathan J. Smith, MD, professor of pediatrics.

I thank Steven G. Scott, DO, professor of physical medicine, Department of Physical Medicine and Rehabilitation, Mayo Clinic and Foundation, Rochester, Minn, for review and discussion of this manuscript.

References

1. Shaffer TE; The uniqueness of the young athlete: Introductory remarks. *Am J Sports Med* 1980;8:370-371.
2. Garrick JG, Requa RK: Injuries in high school sports. *Pediatrics* 1978;61:465-469.
3. Micheli LJ: Overuse injuries in children's sports: The growth factor. *Orthop Clin North Am* 1983;14:337-360.
4. Martens R: The uniqueness of the young athlete: Psychologic considerations. *Am J Sports Med* 1980;8:382-385.
5. Smith NJ: Medical issues in sports medicine. *Pediatr Rev* 1981;2:229-237.
6. Tanner JM: *Growth at Adolescence: With a General Consideration of the Effects of Hereditary and Environmental Factors Upon Growth and Maturation From Birth to Maturity*, ed 2. Boston, Blackwell Scientific Publications Inc, 1962.
7. Hafner JK, Scott SE, Veras G, et al: Interscholastic athletics: Method for selection and classification of athletes. *NY State J Med* 1982;82:1449-1459.
8. Kreipe RE, Gewanter HL: Physical maturity screening for participation in sports. *Pediatrics* 1985;75:1076-1080.
9. Malina RM: Growth of muscle tissue and muscle mass, in Falkner F, Tanner JM (eds): *Human Growth*, ed 2. New York, Plenum Publishing Corp, 1986, vol 2, pp 77-99.
10. Pollock ML, Schmidt DH, Jackson AS: Measurement of cardiorespiratory fitness and body composition in the clinical setting. *Compr Ther* 1980;6:12-27.
11. Thorland WG, Johnson GO, Tharp GD, et al: Validity of anthropometric equations for the estimation of body density in adolescent athletes. *Med Sci Sports Exerc* 1984;16:77-81.
12. AAHPERD Technical Manual: *Health-Related Physical Fitness Test*. Washington, DC, American Alliance for Health, Physical Education, Recreation, and Dance, 1980, pp 20-22.
13. Tanner JM, Davies PSW: Clinical longitudinal standards for height and weight velocity for North American children. *J Pediatr* 1985;107:317-329.
14. Stolz HR, Stolz LM: *The Somatic Development of Adolescent Boys: A Study of the Growth of Boys During the Second Decade of Life*. New York, Macmillan Publishing Co Inc, 1951.
15. Carron AV, Bailey DA: Strength development in boys from 10 through 16 years. *Monogr Soc Res Child Dev* 1974;39:1-37.

In Other AMA Journals

JAMA

Mortality in Infants Discharged From Neonatal Intensive Care Units in Georgia

D. M. Allen; J. W. Buehler; B. N. Samuels; A. W. Brann, Jr (*JAMA*. 1989;261:1763-1766)

Long-term Follow-up of Infants Discharged From Neonatal Intensive Care Units

M. C. McCormick (*JAMA*. 1989;261:1676-1772)

Connaught DTP Special Service

Dependable Delivery Service

Just dial toll-free
1-800-VACCINE
(1-800-822-2463)
from 8AM to 8PM

Temperature-controlled Shipping

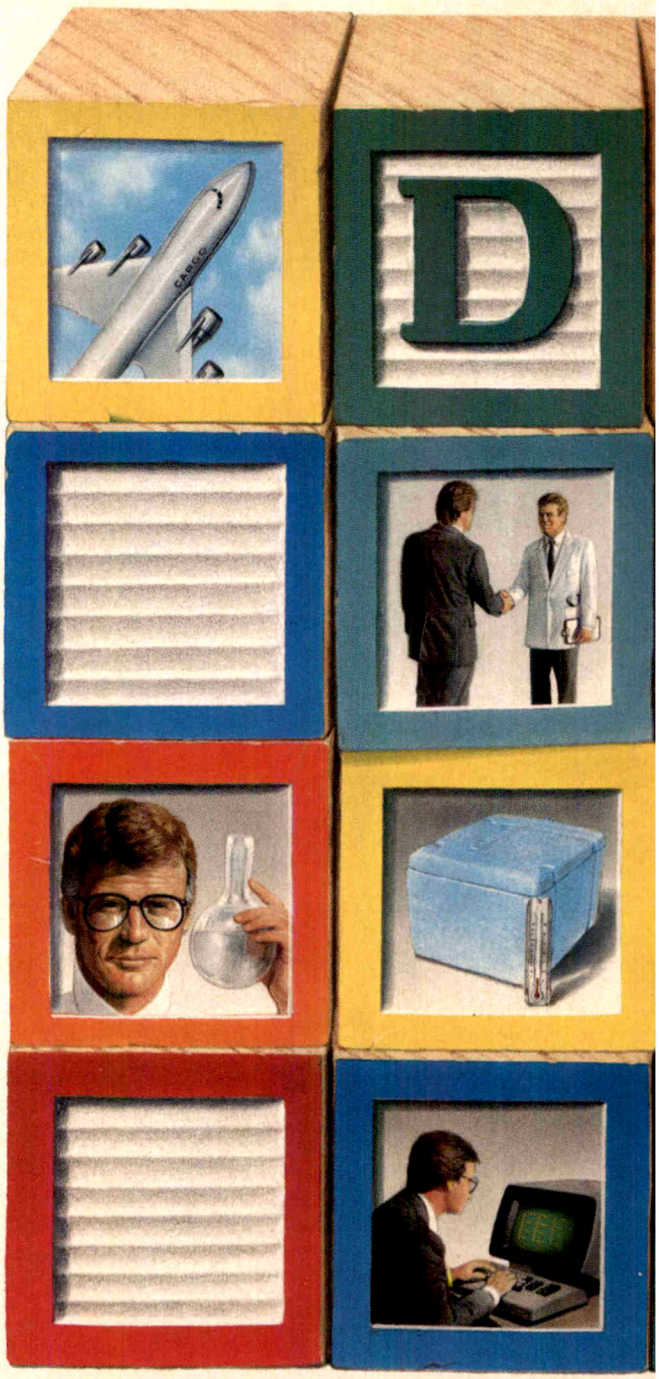
Product integrity ensured
on a year-round basis
through special temperature
indicator and insulated
packaging

Physician Support Materials

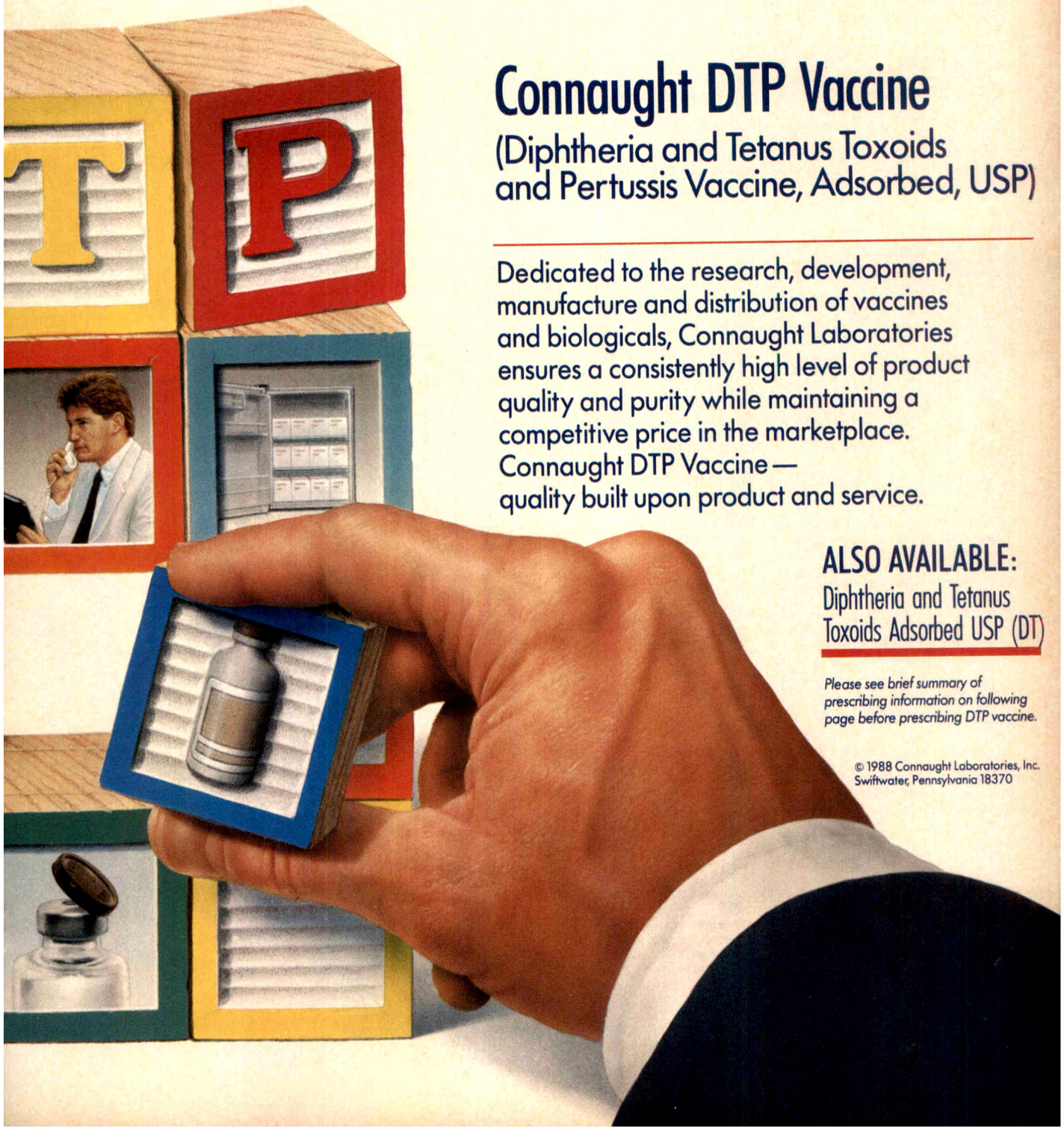
Vaccine Monitoring Kit
to simplify compliance
with the National
Childhood Vaccine Injury Act

® CONNAUGHT LABORATORIES, INC.

pecialist in vaccines and biologicals



BUILDING BLOCKS FOR CHILDREN'S HEALTH



Connaught DTP Vaccine

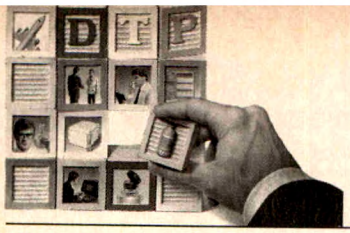
(Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, USP)

Dedicated to the research, development, manufacture and distribution of vaccines and biologicals, Connaught Laboratories ensures a consistently high level of product quality and purity while maintaining a competitive price in the marketplace. Connaught DTP Vaccine — quality built upon product and service.

ALSO AVAILABLE:
Diphtheria and Tetanus Toxoids Adsorbed USP (DT)

Please see brief summary of prescribing information on following page before prescribing DTP vaccine.

© 1988 Connaught Laboratories, Inc.
Swiftwater, Pennsylvania 18370



Connaught DTP Vaccine

(Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Adsorbed, USP)

BRIEF SUMMARY

Before prescribing, please consult the complete package circular.

INDICATIONS AND USAGE: For active immunization of infants and children to age 7 years against diphtheria, tetanus and pertussis (whooping chough) simultaneously. DTP is recommended for primary immunization of infants and children up to 7 years of age. However, in instances where the pertussis vaccine component is contraindicated, or where the physician decides that pertussis vaccine is not to be administered, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) should be used. Immunization should be started at 6 weeks to 2 months of age and be completed before the seventh birthday.

CONTRAINDICATIONS: *Persons 7 years of age and older must NOT be immunized with Pertussis Vaccine.*

Absolute contraindications.

1. Allergic hypersensitivity to any component of the vaccine.
2. Fever of 40.5°C (105°F) or greater within 48 hours.
3. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
4. Persisting, inconsolable crying lasting 3 hours or more or an unusual, high-pitched cry occurring within 48 hours.
5. Convulsion(s) with or without fever occurring within 7 days.
6. Encephalopathy occurring within 7 days; this includes severe alterations in consciousness with generalized or local neurologic signs.

The presence of a neurologic condition characterized by changing developmental or neurologic findings, regardless of whether a definitive diagnosis has been made, is also considered an absolute contraindication to receipt of pertussis vaccine, because administration of DTP may coincide with or possibly even aggravate manifestations of the disease. Such disorders include uncontrolled epilepsy, infantile spasms, and progressive encephalopathy.

Use of this product is also contraindicated if the child has a personal or family history of a seizure disorder. However, the ACIP does not accept family histories of convulsions or other central nervous system disorders as contraindications to pertussis vaccination.

IT IS ALSO A CONTRAINDICATION TO ADMINISTER DTP TO INDIVIDUALS KNOWN TO BE SENSITIVE TO THIMEROSAL. IN ANY CASE, EPINEPHRINE INJECTION (1:1000) MUST BE IMMEDIATELY AVAILABLE SHOULD AN ACUTE ANAPHYLACTIC REACTION OCCUR DUE TO ANY COMPONENT OF THE VACCINE.

Elective immunization procedures should be deferred during an outbreak of poliomyelitis.

WARNINGS: *This vaccine must NOT be used for immunizing persons 7 years of age and older.*

IMMUNIZATION SHOULD BE DEFERRED DURING THE COURSE OF ANY ACUTE ILLNESS. THE OCCURRENCE OF ANY TYPE OF NEUROLOGICAL SYMPTOMS OR SIGNS, INCLUDING ONE OR MORE CONVULSIONS (SEIZURES) FOLLOWING ADMINISTRATION OF THIS PRODUCT IS AN ABSOLUTE CONTRAINDICATION TO FURTHER USE. USE OF THIS PRODUCT IS ALSO CONTRAINDICATED IF THE CHILD HAS A PERSONAL OR FAMILY HISTORY OF A SEIZURE DISORDER.

THE PRESENCE OF ANY EVOLVING OR CHANGING DISORDER AFFECTING THE CENTRAL NERVOUS SYSTEM IS A CONTRAINDICATION TO ADMINISTRATION OF DTP REGARDLESS OF WHETHER THE SUSPECTED NEUROLOGICAL DISORDER IS ASSOCIATED WITH OCCURRENCE OF SEIZURE ACTIVITY OF ANY TYPE.

The administration of DTP to children with proven or suspected underlying neurological disorders, must be decided on an individual basis. Please refer to ACIP recommendations for the following categories of patients:

1. **Infants as yet unimmunized who are suspected of having underlying neurologic disease.**
2. **Infants and children with neurologic events temporally associated with DTP.**
3. **Incompletely immunized children with neurologic events occurring between doses.**
4. **Infants and children with stable neurologic conditions.**
5. **Children with resolved or corrected neurologic disorders.**

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Short-term (less than 2 weeks) corticosteroid therapy or intra-articular, bursal, or tendon injections with corticosteroids should not be immunosuppressive. Although no specific studies with pertussis vaccine are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for one month, otherwise, the patient should be vaccinated while still on therapy.

Persons receiving immunosuppressive therapy, a recent injection of immune globulin, or having an immunodeficiency disorder, may not generate an adequate immunologic response to the DTP vaccine.

DTP should not be given to infants or children with any coagulation disorder that would contraindicate intramuscular injection, unless the potential benefit clearly outweighs the risk of administration.

The simultaneous administration of DTP, oral polio virus vaccine (OPV), and/or measles-mumps-rubella vaccine (MMR) has resulted in seroconversion rates and rates of side effects similar to those observed when the vaccines are administered separately. Please refer to ACIP recommendations.

PRECAUTIONS

GENERAL

Epinephrine injection (1:1000) must be immediately available should an acute anaphylactic reaction occur due to any component of the vaccine.

Prior to an injection of any vaccine, all known precautions should be taken to prevent side reactions. This includes a review of the patient's history with respect to possible sensitivity and any previous adverse reactions to the vaccine or similar vaccines (see CONTRAINDICATIONS), and a current knowledge of the literature concerning the use of the vaccine under consideration.

The vial of vaccine should be vigorously shaken to ensure a proper suspension of the antigen and adjuvant.

Special care should be taken to ensure that the injection does not enter a blood vessel.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another.

ADVERSE REACTIONS

Not all adverse events following administration of DTP are causally related to DTP vaccine.

Adverse reactions which may be local and include pain, erythema, heat, edema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria, tetanus, or pertussis antigens. Some data suggest that febrile reactions are more likely to occur in those who have experienced such responses after prior doses. However, these observations were not noted by Barkin, R.M., et al. Occasionally, a nodule may be palpable at the injection site of adsorbed products for several weeks. Sterile abscesses at the site of injection have been reported (6-10 per million doses).

Mild systemic reactions, such as fever, drowsiness, fretfulness, and anorexia, occur quite frequently. These reactions are significantly more common following DTP than following DT, are usually self-limited, and need no therapy other than, perhaps, symptomatic treatment (e.g., antipyretics). Rash, allergic reactions, and respiratory difficulties, including apnea, have been observed.

Moderate to severe systemic events, such as fever of 40.5°C (105°F) or higher, persistent, inconsolable crying lasting 3 hours or more, unusual high-pitched crying, collapse, or convulsions, occur relatively infrequently. More severe neurologic complications, such as a prolonged convulsion or an encephalopathy, occasionally fatal, have been reported to be associated with DTP administration.

Approximate rates for adverse events following receipt of DTP vaccine (regardless of dose number in the series) are indicated in Table 1.

TABLE 1. Adverse events occurring within 48 hours of DTP immunizations

Event	Frequency*
Local	
Redness	1/3 doses
Swelling	2/5 doses
Pain	1/2 doses
Mild/moderate systemic	
Fever >38°C (100.4°F)	1/2 doses
Drowsiness	1/3 doses
Fretfulness	1/2 doses
Vomiting	1/15 doses
Anorexia	1/5 doses
More serious systemic	
Persistent, inconsolable crying (duration ≥3 hours)	1/100 doses
High-pitched, unusual cry	1/900 doses
Fever ≥40.5°C (≥105°F)	1/330 doses
Collapse (hypotonic-hyporesponsive episode)	1/1,750 doses
Convulsions (with or without fever)	1/1,750 doses
Acute encephalopathy†	1/110,000 doses
Permanent neurologic deficit†	1/310,000 doses

*Number of adverse events per total number of doses regardless of dose number in DTP series.
†Occurring within 7 days of DTP immunization.

The frequency of local reactions and fever following DTP vaccination is significantly higher with increasing numbers of doses of DTP, while other mild to moderate systemic reactions (e.g., fretfulness, vomiting) are significantly less frequent. If local redness of 2.5 cm or greater occurs, the likelihood of recurrence after another DTP dose increases significantly.

Although there are uncertainties in the reported studies, recent data suggest that infants and young children who have had previous convulsions (whether febrile or nonfebrile) are more likely to have seizures following DTP than those without such histories.

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.

Sudden infant death syndrome (SIDS) has occurred in infants following administration of DTP. A large case-control study of SIDS in the United States showed that receipt of DTP was not causally related to SIDS. It should be recognized that the first three primary immunizing doses of DTP are usually administered to infants 2–6 months old and that approximately 85% of SIDS cases occur at ages 1–6 months, with the peak incidence occurring at 6 weeks–4 months of age. By chance alone, some SIDS victims can be expected to have recently received vaccine.

Onset of infantile spasms has occurred in infants who have recently received DTP or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DTP or DT was not causally related to infantile spasms. The incidence of onset of infantile spasms increases at 3–9 months of age, the time period in which the second and third doses of DTP are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of DTP.

Reporting of Adverse Events

Reporting by parents and patients of all adverse events occurring within 4 weeks of antigen administration should be encouraged.

The following illnesses have been reported as temporally associated with the vaccine; neurological complications including cochlear lesion, brachial plexus neuropathies, paralysis of the radial nerve, paralysis of the recurrent nerve, accommodation paresis, and EEG disturbances with encephalopathy. In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.

Product information as of July, 1986

® CONNAUGHT® is a trademark owned by Connaught Laboratories, Inc.

Mfd. by: CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370, U.S.A.
MKT0246 12/88
Printed in U.S.A. 0585

Smoking Policy in Pediatric Hospitals and Wards

Jerri Ann Jenista, MD

• **The American Academy of Pediatrics has recommended that pediatricians take the lead in banning cigarette smoking in all pediatric health care facilities. This study investigated the use of "nonsmoking" policies and their planned revisions, problems in enforcement, and any history of challenges to restrictive or lenient policies. The surveys were mailed to 329 hospitals affiliated with pediatric training programs as the institutions most likely to attempt to comply with the American Academy of Pediatrics recommendations. Representatives from 199 (60%) of the programs responded. The programs had a range of 12 to 350 pediatric beds in children's hospitals (27%), pediatric wards (69%), or general hospitals (4%). Only nine hospitals were "smoke-free," ie, having no designated indoor area for smoking. Another 35 had "restrictive" policies allowing smoking in only a single site or two preselected sites. Pediatric hospitals or wards were no more likely to have smoke-free policies than general hospitals. Existence of smoke-free or restrictive policies was unrelated to any other factor examined. Smoke-free and restrictive policies were more likely to be rigorously enforced but not more likely to engender formal challenges. Although almost all policies had been recently or are being revised, pediatric hospitals and wards remain remiss in controlling childhood smoke exposure.**

(*AJDC*. 1989;143:567-569)

The Committee on Environmental Hazards of the American Academy of Pediatrics has recommended that pediatricians take the lead in banning cigarette smoking in all pediatric hospitals and facilities caring for children.[1] In an effort to discover how widespread such "nonsmoking" policies are, I conducted a questionnaire study examining current policies, planned revisions, enforcement problems, and any challenges to restrictive or lenient policies in hospitals caring for children in the United States.

METHODS

Hospitals affiliated with pediatric residency training programs were selected for study because they are most likely to have the following: (1) physically defined pediatric wards, (2) a sufficient number of pediatric patients to have considered smoking policies specific for pediatrics, and (3) strong advocates for more restrictive pediatric policies than hospitals without a specific department of pediatrics.

When studied, 329 residency training program affiliated hospitals existed in the United States and Puerto Rico.[2]

A simple three-page questionnaire was mailed to the public relations department of each hospital in November 1986. A self-addressed stamped envelope was enclosed for returning the form. In addition, I asked each hospital for a copy of any existing written smoking policy. The questionnaire was not anonymous and the hospitals were given the option to receive the study results, if desired. A second questionnaire was sent to nonrespondents in April 1987.

Data analysis consisted of simple descriptive statistics, cross-tabulations, and χ^2 tests using the statistical analysis programs of CLINFO Plus (Bolt Beranek Newman Software Products Corp, Boston, Mass, 1986).

RESULTS

One hundred twenty-six questionnaires were returned from the first mailing and an additional 71 from the second mailing. Two hospitals indicated that they no longer had residency training program affiliations, giving an overall response rate of 60% (199/329).

Respondent Characteristics

Table 1 describes the characteristics of the hospitals replying to the survey. All but 6 had a written smoking policy; 1 did not answer the question. Policies had been in effect for less than 6 months, 28 (15%); 6 months to 2 years, 67 (35%); longer than 2 years, 89 (47%); unknown, 7 (4%). Seventy-six (40%) hospitals had revised their policies within the past year, 45 (24%) were in the revision process, 14 (7%) were considering revisions, and 53 (28%) did not contemplate any changes. Pediatric hospitals were no more likely than pediatric wards or general hospitals to have a policy either recently revised or in revision now.

Regulatory Influences

The policy was written specifically for the children's hospital or pediatric ward in 28% (54 hospitals). General hospital or university policy covered another 68% (131 hospitals), and 4% (8) of the hospitals were covered by a military policy. Smoking policies were based, wholly or partially, on city or municipal regulations, 44 hospitals (22%); state law, 70 hospitals (36%); university or military policy, 29 hospitals (15%); and/or another regulating body apart from hospital administration, 34 hospitals (17%). Smoking policy for hospital-associated "home-away-from-home" or Ronald McDonald facilities was the same as the hospital ward in 11 hospitals (15%), developed separately for that building in 52 hospitals (69%), or did not exist in 11 hospitals (15%).

Severity of Policy

Only 16 hospitals (8%) considered themselves smoke-free. If smoke-free is defined as "no designated indoor area for smoking," then 9 hospitals were smoke-free. Smoke-free hospitals were no more likely to designate an outdoor smoking area than the rest of the group (6 of 9 vs 109 of 188), $P>.05$. In addition to the 9 smoke-free hospitals, another 35 had "restrictive" policies allowing smoking in only a single site (16) or two

Accepted for publication December 13, 1988.

From the Department of Pediatrics and Communicable Diseases, C. S. Mott Children's Hospital, University of Michigan, Ann Arbor.

Presented in part at the Region 5 annual meeting of the Ambulatory Pediatric Association, Chicago, October 15, 1987.

Reprints not available.

Table 1.—Characteristics of Pediatric Programs Responding to Smoking Policy Survey (n = 196)

	No. or Range (% or Median)
Children's hospitals, %	54 (27)
Free standing	29 (55)
Physically part of a larger institution	10 (19)
Physically separate but within a larger complex of hospital buildings	14 (26)
Geographic area of a larger hospital (pediatric wards), %	135 (69)
General hospital without designated pediatric areas, %	7 (4)
Pediatric beds (excluding normal newborns)	12-350 (63)
Annual admissions	100-36 500 (2674)
Normal newborn bassinettes	0-250 (35)
Annual normal newborn admissions	0-18 000 (2500)
Programs with either or both a pediatric outpatient department or emergency clinic, %	190 (96)
Ronald McDonald House or equivalent "home away from home" for families, %	101 (53)

Table 2.—Areas Designated as Smoking Areas in Hospitals Caring for Children (n = 197)

Access Areas	No. (%)
Public or visitor	
Special section of a cafeteria or vending area	135 (69)
Gardens or courtyards outside the building	105 (53)
Special smoking waiting rooms	96 (49)
Public lobbies or corridors	62 (31)
General cafeteria or vending area	54 (27)
General waiting rooms	54 (27)
General intensive care waiting areas	40 (20)
Special smoking intensive care waiting areas	39 (20)
Designated smoking area outside the building	20 (10)
Patient	
Special smoking patient lounges	49 (25)
General patient rooms	41 (21)
General patient lounges	31 (16)
Special smoking patient rooms	28 (14)
Employee	
Private offices	127 (64)
Staff lounges	86 (44)
Special smoking staff lounges	49 (25)
Common staff areas (conference or classrooms)	30 (15)

preselected sites (19). Pediatric hospitals or wards were no more likely to have smoke-free or restrictive policies than general hospitals without designated pediatric beds. Having a smoke-free or restrictive policy was unrelated to the number of pediatric beds or admissions, the type of pediatric hospital, liaison with a Ronald McDonaldlike house, age of the policy, recent or ongoing revisions of policy, or the presence of outside statutes or regulations.

Extent of Policy

With few exceptions, the policy applied to all patients, parents, visitors, and employees. In general, the policy covered inpatient (99%), outpatient (91%), and emergency (89%) facilities. Only four (2%) hospitals did not have designated smoking areas. Designated smoking areas in the remaining hospitals are listed in Table 2.

Patient Smoking

Forty hospitals (20%) allowed any patient to smoke, while 21 hospitals (11%) restricted smoking only to patients older than 18 years. Seventy-five hospitals (38%) allowed smoking only with physician permission. Another 3 hospitals (2%) allowed only psychiatric patients to smoke; 1 required physician permission even for those patients. Sixteen hospitals (8%) prohibited smoking by any patient. Forty-one hospitals (21%) reported no policy on patient smoking. Smoking by pediatric patients was banned in 22 (41%) of the pediatric hospitals, 36 (27%) of the pediatric wards, and 1 general hospital(14%).

Publicity

Smoking policies were made public in these facilities by one or more of the following: signs, 182 (92%); brochures, 97 (49%); newspaper, television, or other media publicity, 18 (9%); or other means such as verbal reminders at hospital admission or employee orientation, hospital cable television, or employee memos, 39 (20%).

Penalties for Infractions

Reported penalties for infractions of smoking policy varied. Patients were asked to leave nonsmoking areas, 116 (59%); received a visit from a security or administrative officer, 31 (16%); or suffered some other penalty such as notification of attending physician or warning of hospital discharge, 26 (13%). Visitors were asked to leave nonsmoking areas, 148 (75%); were asked to leave the building, 22 (11%); were denied a visitors pass, 7 (4%); or suffered another penalty such as a nontraffic citation or court summons, 22 (11%). Employees were asked to leave nonsmoking areas, 118 (60%); incurred a disciplinary measure such as suspension after repeated infractions, 78 (40%); or suffered some other penalty such as a fine or prosecution under local or state ordinances, 13 (7%).

Enforcement

Responsibility for enforcement of the policy fell on employees, 163 (83%); security personnel, 74 (38%); hospital administrators, 54 (43%); or others such as volunteers, 12 (6%). Policies were enforced with varying rigor, ranging from very strictly (stringent penalties), 27 (14%); strictly (penalties not enforced), 53 (28%); semistrict (some areas but not others), 64 (34%); loosely (no penalties), 34 (18%); to essentially ignored, 10 (5%). Both smoke-free and restrictive policies were more likely to be very strictly or strictly enforced ($P = .001$).

Challenges

Only 59 hopitals (30%) had received any formal challenges to the smoking policy. These came from individual employees, 34 (43%); members of the public or patients, 27 (39%); employee unions, 6 (8%); or others such as public interest groups or physicians, 12 (15%). All but a few of the challenges were resolved by the hospital administration. In only one case each was a nonhospital arbitration body or the legal system involved.

Although policies that were loosely enforced or ignored were more often challenged (43%) than strict or very strictly enforced policies (23%), the difference was not statistically significant. Smoke-free and restrictive policies were no more likely to have been challenged more frequently or ever. Pediat-

ric hospitals were no more likely than pediatric wards or general hospitals to rigorously enforce their policies.

Questionnaire Accuracy

Representatives of 48 hospitals returned copies of their hospital's smoking policy with the questionnaire. Answers to the survey questions accurately reflected the stated policy except for the area of penalties for infractions. Written policies frequently cited specific penalties, usually employee disciplinary action or prosecution under city or state law, but only a few of those were listed on the survey. Fifty-nine hospitals requested a copy of the survey results.

COMMENT

Despite the American Academy of Pediatrics recommendation and considerable national social pressure to prevent childhood exposure to smoke, medical institutions dedicated to the care of children fall short of that goal. Although two thirds of the hospitals surveyed were in the revision process or had completed a revised smoking policy within the year preceding the survey, still only 25% (49 hospitals) were either smoke-free or severely restricted. By written policy, 40 hospitals would theoretically allow even a child to smoke.

Pediatric hospitals dedicated solely to the care of children, whether physically separate from other hospital or institutional buildings, also showed a poor record of prohibiting smoke exposure. Policies in those hospitals were no more restrictive or strictly enforced than in pediatric wards or beds that were part of larger general hospitals. Neither did numbers of children involved affect the severity of the policy. In other words, having a particular concern for children, even large numbers of children, was not reflected in a concern for their exposure to smoke.

Disappointingly, the existence of nonhospital regulations, be they military, city or state, university or church mandated, was not associated with the presence of either smoke-free or restrictive policies. Such regulations are most likely meant to provide minimum standards of clean air for public buildings and, thus, are insufficiently proscriptive for the hospital setting.

For example, Denver City Ordinance No. 117 states "In hospitals and health facilities, all patient areas shall be designated as no smoking areas. . . ."[3] Denver Children's Hospital, in direct response to this ordinance, revised its policy restricting smoking for parents and visitors to areas of the snack bar and cafeteria and the intensive care unit waiting area. In addition, employees are permitted to smoke in the same eating areas and certain lounges and offices. Children, hospitalized or not, have access to all the designated parent smoking areas.[4]

That it is not administratively impossible to have a smoke-free or a severely restrictive policy is indicated by the answers about enforcement. Hospitals with such policies were *more* likely to report "very strict" or "strict" enforcement in actual practice but did not report an increased frequency of formal challenges.

CONCLUSION

Pediatricians have not yet attained their goal of banning cigarette smoking in all pediatric hospitals. The degree of cooperation with this study and the number of programs requesting survey results indicate that considerable interest in the topic exists. Clean air legislation, although serving as an impetus to revise outdated policies, is apparently insufficient to mandate protection of children from cigarette smoke while in hospitals. Pediatricians cannot rely on regulations formulated for the general public health to produce adequate smoke protection for children.

A model policy for all pediatric hospitals and wards should be restrictive, and easy to understand, communicate, and enforce. What better example than that of the Loma Linda (Calif) University Medical Center? "Smoking is prohibited inside the Medical Center by any person, in any place, under any condition."[5]

This investigation was supported in part by Public Health Service Clinical Research Center grant 5M01-RR0042-25 to the University of Michigan, Ann Arbor. Part of this was published as an abstract in Pediatric Research (1987;21:258A).

References

1. American Academy of Pediatrics. Involuntary smoking—a hazard to children. *Pediatrics.* 1986;77:755-757.
2. American Medical Association. *Directory of Residency Training Programs.* Chicago, Ill: American Medical Association; 1986:265-278.
3. Denver City Ordinance 117 (March 3, 1986).
4. The Childrens Hospital, Denver V-020 (Rev April 1986).
5. LOMA LINDA UNIVERSITY MEDICAL CENTER CODE A-16 (effective June 1985).

In Other AMA Journals

JAMA

The Use of Anencephalic Infants as Organ Sources
D. A. Shewman; A. M. Capron; W. J. Peacock; B. L. Schulman (*JAMA.* 1989;261:1773-1781)

Congenital Syphilis and Necrotizing Funisitis
R. M. Fojaco; G. T. Hensley; L. Moskowitz (*JAMA.* 1989;261:1788-1790)

Ebstein's Anomaly and Extracardiac Defects

Joseph R. Siebert, PhD; Mason Barr, Jr, MD; J. Craig Jackson, MD; Denis R. Benjamin, MB, BCh

• Ebstein's anomaly of the tricuspid valve occurs as an isolated defect with other forms of congenital heart disease such as transposition of the great arteries or tetralogy of Fallot or, rarely, in association with extracardiac malformations. Because so little is known about this latter group, we studied four cases clinically, at autopsy, and by means of a retrospective chart review. Major extracardiac changes most often involved the craniofacial region, central nervous system, and limbs. Karyotypes were normal, and no distinctive syndromes or anatomic patterns were identified. Since the timing of Ebstein's anomaly is quite precise, ascertainment of such cases on the basis of cardiac morphology may enhance the understanding of etiology and pathogenesis. Both causes and mechanisms may well be diverse, for the clinical histories and anatomic findings in present and previously reported cases vary considerably. Isolated Ebstein's anomaly may develop from topographically and temporally localized damage. Ebstein's anomaly with extracardiac defects may involve damage during a longer, and perhaps earlier, period.

(*AJDC.* 1989;143:570-572)

The association of cardiac and extracardiac anomalies has at times been explained on a pathogenetic or etiologic basis. Recent examples involve abnormalities in the cephalic neural crest, in which several conditions, such as DiGeorge sequence, CHARGE association, fetal alcohol syndrome, and isotretinoin embryopathy, show defects in the conotruncal region of the heart, aortic arches, skeletal components of the head, and tissues derived from the branchial arches.[1-4] By contrast, the association of most other cardiac anomalies with extracardiac defects is poorly understood.

Ebstein's anomaly of the tricuspid valve is one such example. The defect was first described by Ebstein[5] in 1866 and generally occurs in isolated fashion, without extracardiac defects. Several hundred cases have been reported, and a number of reviews are available.[6-8] The malformation occurs in 1 in 20 000 to 1 in 50 000 live births and in 0.5% of infants with congenital heart disease.[9] Ebstein's anomaly has been described as "congenital downward displacement of the tricuspid valve" or "atrialization of the right ventricle." These phrases, coined relatively early in the study of malformed hearts, form succinct, if somewhat incomplete, images of the anomaly. A more precise anatomic definition of Ebstein's anomaly is now available:

> The two characteristic features are redundancy of valve tissue and adherence of a variable portion of the medial (septal) and posterior cusps to the right ventricular wall, resulting in an origin of the free portion of the valve cusp from the right ventricular wall some distance away from the atrial ventricular junction.[10]

The anomaly forms a continuum of pathologic changes, but has certain features in common. The posterior and septal leaflets arise from the ventricular wall inferior to the atrioventricular junction, thus giving the appearance of being downwardly displaced. Valve leaflets are also redundant, chordae tendineae are short, and papillary muscles are deformed. Insertions of distal portions of leaflets are also abnormally low. A region in the right ventricle proximal to the tricuspid valve may be thin, aneurysmally dilated, and, in these ways, resemble the atrium.[8,11,12] Pressures within this region may also be atrial, while electric impulses are ventricular and generally abnormal,[13] although they are infrequently normal.[14]

We describe four patients with Ebstein's anomaly of the tricuspid valve and additional, extracardiac malformations. The study of such patients may provide ways of further determining pathogenetic and etiologic factors.

PATIENT REPORTS

PATIENT 1.—A white female infant was born at 36 weeks of gestation with hypertelorism, epicanthal folds, low-set posteriorly rotated ears, a cleft uvula, and medially rotated hands (Fig 1). Chest roentgenography, electrocardiography, and echocardiography revealed Ebstein's anomaly and Wolff-Parkinson-White arrhythmias. In addition, the infant was deaf and blind and manifested cerebral palsy with spastic diplegia and seizures. These findings, and profoundly delayed growth and development, initially suggested the diagnosis of Aicardi's syndrome (agenesis of corpus callosum, abnormal electroencephalogram, mental retardation, flexion spasms, and skeletal defects[15-17]). Ophthalmic examination, however, revealed no structural anomalies of the eyes, and electroencephalography showed no infantile spasms or hypsarrhythmias. The infant was followed up until she was 16 months old, when she developed bronchopneumonia and cardiac failure and died. At postmortem examination, Ebstein's anomaly was apparent, with a low-set tricuspid valve, focal parachutelike dilatations of valvular tissue, and short, opacified chordae tendineae. The right atrium and ventricle were dilated and hypertrophied, and the supravalvular portion of the right ventricle was thin walled. Several changes were apparent in the brain, including asymmetry of the cerebral hemispheres, polymicrogyria, unilateral hydrocephalus, and agenesis of the corpus callosum. In addition, the right lung was bilobed, the thymus was partly behind the left innominate vein and without right lobes, the cecum was mobile, and the uterus was unicornous. No specific syndromic delineation was made clinically or at autopsy. The patient's karyotype was 46,XX. Maternal history was as follows: The 24-year-old, gravida 4, para 1 mother had had two spontaneous abortions; both occurred in the second month and were unexplained. One 4-year-old sibling was normal. Maternal blood pressure was elevated during the pregnancy. Findings of an ultrasound examination, performed at 6 to 7 weeks because of spotting, were unremarkable. Diphenoxylate hydrochloride with atropine sulfate (Lomotil) was taken for several episodes of diarrhea at 10 weeks. No history of unusual exposures was elicited.

PATIENT 2.—A 3250-g white female infant was born to a 29-year-old primigravida after a term gestation. Bilateral cysts in the choroid plexus and possible hydrocephalus had been diagnosed prenatally by ultrasound. At birth, the infant was cyanotic and in respiratory distress, requiring intubation. Several external anomalies were noted, including a narrow anterior cranium with parietal bossing, hypotelorism, beaked nose, arachnodactyly, and camptodactyly (Fig 2). The infant suffered intractable renal, hepatic, and cardiac failure and died of pulmonary congestion, anasarca, ascites, and bronchopulmon-

Accepted for publication January 9, 1989.

From the Departments of Pathology (Drs Siebert and Benjamin), Laboratory Medicine (Dr Benjamin), and Pediatrics (Drs Jackson and Benjamin), Children's Hospital and Medical Center and University of Washington, Seattle, and the Teratology Unit, Department of Pediatrics, C. S. Mott Children's Hospital and University of Michigan, Ann Arbor (Dr Barr).

Presented in part at the annual meeting of the Teratology Society, Palm Springs, Calif, June 17, 1987.

Reprint requests to Department of Laboratories, Children's Hospital and Medical Center, PO Box C-5371, Seattle, WA 98105 (Dr Siebert).

Fig 1.—Patient with epicanthal folds, posteriorly rotated ears, and delayed growth (patient 1).

Fig 2.—Narrow anterior cranium, parietal bossing, hypotelorism, and beaked nose are evident (patient 2).

Fig 3.—Ventral aspect of fetus with 1-cm-long umbilical cord, omphalocele, exstrophy of the urinary bladder, and malformed limbs (patient 4).

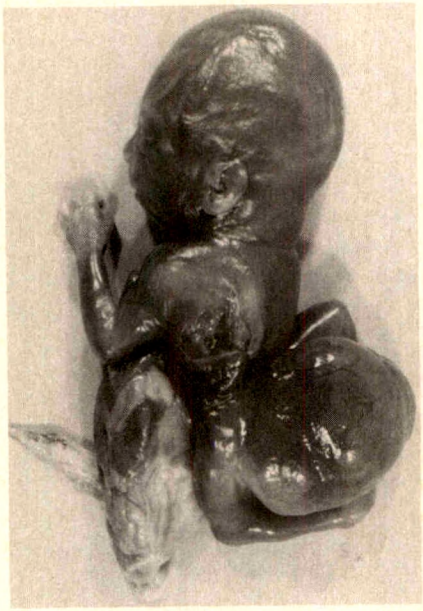


Fig 4.—Dorsal view, showing angulated spine and myelocystocele (patient 4).

ary dysplasia at 3 weeks of age. At autopsy, several defects were noted: Ebstein's anomaly, with displaced tricuspid valve, marked nodular thickening, and short chordae; dilated lateral ventricles of the brain; cysts of the choroid plexus; and hypoplasia of the corpus callosum. The karyotype was 46,XY. No history of unusual exposures or other prenatal occurrences was given.

PATIENT 3.—A white male infant was born at term to a 23-year-old primigravida. Ultrasonography 1 week prior to delivery revealed cardiomegaly, and results of fetal echocardiography suggested the diagnosis of Ebstein's anomaly. Elective delivery was by cesarean section for fetal distress. At birth, the infant was malodorous and weighed 3580 g. Despite resuscitation, he remained acidotic and hypoxic. Cultures were positive for group B streptococcus. The infant lived only 4 days, dying of severe fibrosing bronchiolitis. At autopsy, the major defect was Ebstein's anomaly. The right atrium was large and contained a small secundum atrioseptal defect, the supravalvular portion of the right ventricle was very thin and "atrialized," and the left ventricle was markedly hypertrophic. Several minor anomalies were also noted: the neck was short, eight ribs articulated with the sternum on the right, and the uvula was bilobed. No familial, teratogenic, or other pertinent history was given.

PATIENT 4.—A 279-g white male fetus was stillborn at 19 to 20 weeks of gestation. The mother was a 32-year-old, gravida 4, para 3 woman whose pregnancy was terminated because of elevated serum α-fetoprotein levels, which resulted in the initial referral and workup, and because ultrasonography of the fetus revealed a large omphalocele, severe angulation of the spine near the pelvis, and malformed limbs. An additional mass, perhaps not attached to the fetus, was suspected. Postmortem examination showed a severely malformed midgestational fetus with a narrow, deep chest (Fig 3). A large omphalocele held virtually all abdominal organs and bordered an extrophic bladder. The umbilical cord was 1 cm long and contained only the right artery. External genitalia consisted of a single cutaneous nubbin on the upper medial thigh; the anus was imperforate. Scoliosis was marked, but without vertebral segmentation defects, and a myelocystocele was present (Fig 4). Eight ribs articulated with the sternum bilaterally; a xiphoid process was not identified. The feet were altered by equinovarus deformity on the left, and calcaneovalgus on the right. Examination of the heart revealed Ebstein's anomaly, right atrial dilatation, and "atrialization" of the proximal right ventricle. The left kidney and ureter were absent. The brain was grossly normal, without Arnold-Chiari malformation or hydrocephalus. The karyotype was 46,XY. No abnormal history was elicited.

COMMENT

Different mechanisms have been proposed for the valvular defect in Ebstein's anomaly. Myocardium derives from the visceral coelomic wall and is initially separated from endocardium by cardiac jelly, the substance that comprises endocardial cushions. Engle et al[18] proposed that a dysgenetic event occurring at this site could result in Ebstein's anomaly. However, if this is the case, it seems that the defect would have to be both focal and mild, for the body wall, pericardium, and epicardium are not involved in Ebstein's anomaly. Anderson and Lie[19] put forth a different scheme in 1978: The tricuspid leaflets form by delamination from the inner layer of right ventricular myocardium. Changes in the process of delamination could therefore be responsible for the malformation. Whether this event is primary in Ebstein's anomaly is unknown, but in any case, the process seems to be imprecise, for the morphological features of the tricuspid valve in

Ebstein's anomaly vary considerably. Tricuspid development may also be affected by the hemodynamics of the right ventricle. A distorted ventricle could secondarily influence the developing tricuspid valve. The latter concept is supported by the observation of abnormally large cardiac circumferences at the atrioventricular sulcus of hearts with Ebstein's anomaly; this in turn implies earlier distention of the atrioventricular canal.[19]

Causation in Ebstein's anomaly is also understood incompletely, but appears to be heterogeneous. A teratogenic effect seems possible in some cases, for the defect has been linked to the maternal use of lithium.[20,21] The human may be particularly susceptible, for Ebstein's anomaly has not been observed following lithium administration in mice,[22] rats,[23] rabbits, or monkeys.[24] Interestingly, some offspring of mice treated with lithium manifested fused ribs and vertebral defects similar to those observed in the present study.[25-27] The effect of infectious agents is not understood. In the present study, one mother (case 1) may have suffered a transient viremia early in gestation. She was treated with a preparation of diphenoxylate hydrochloride and atropine sulfate, which is not associated with any recognized teratogenesis. The remarkably short umbilical cord in case 4 presumably tethered the infant, resulting in defects of the vertebral column, abdominal wall, and limbs.[28-30] The possibility that such biomechanical phenomena also affected the development of the heart is uncertain, but cannot be ignored. Genetic effects also seem possible, since familial cases have been reported,[31,32] with inheritance described as multifactorial.[9]

The association of Ebstein's anomaly with extracardiac malformations is more difficult to explain. Most defects observed in this study were primary malformations generally thought to arise early in gestation, a relatively remote period that is associated with variable maternal recall. A major reason for ascertaining cases on the basis of morphological features of the heart rather than on other anomalies is that timing in the development of Ebstein's anomaly is precise. The anterior leaflet of the tricuspid valve is formed by 44 to 48 days, a period corresponding to the 15- to 16-mm, stage 18 embryo; the remaining leaflets are just beginning to develop at this time.[33] Since the anterior leaflet is generally spared or less severely altered in Ebstein's anomaly and the leaflets develop in a particular order, one can hypothesize a pathologic event at a specific time, *after* formation of the anterior leaflet, but *before* development of the other two.[34]

If one considers the ways in which cardiac and extracardiac cells might be simultaneously damaged in morphogenesis, several mechanisms seem possible: First, one small parent population of cells could be damaged and give rise secondarily to anomalies in derived tissues. Second, a teratogen might have its primary effect at a critical period of development; several cell populations could be injured at the same time, giving rise to anomalies in multiple systems. Third, a defective gene or genes could affect one or more populations of cells. These points, as well as observations from present and previously reported cases, suggest at least two major modes of pathogenesis: (1) a topographically and temporally localized process may be responsible for the development of isolated Ebstein's anomaly, presumably soon after day 48 of gestation, and (2) damage during an earlier and longer period of vulnerability may result in Ebstein's anomaly with multiple extracardiac defects.

References

1. Kirby ML, Bockman DE. Neural crest and normal development. *Anat Rec.* 1984;209:1-6.
2. Siebert JR, Graham JM Jr, MacDonald C. Pathologic features of the CHARGE association: support for involvement of the neural crest. *Teratology.* 1985;31:331-336.
3. Daft PA, Johnston MC, Sulik KK. Abnormal heart and great vessel development following acute ethanol exposure in mice. *Teratology.* 1986;33:93-104.
4. Webster WS, Johnston MC, Lammer EJ, Sulik KK. Isotretinoin embryopathy and the cranial neural crest: an in vivo and in vitro study. *J Craniofac Genet Dev Biol.* 1986;6:211-222.
5. Ebstein W: Über einen sehr seltenen Fall von Insufficienz der Valvula tricuspidalis: bedingt durch eine angeborene hochgradige Missbildung derselben. *Arch Anat Physiol Wissenchaft Med.* 1866;33:238-254.
6. Schiebler GL, Adams P, Anderson RC, Amplatz K, Lester RG. Clinical study of twenty-three cases of Ebstein's anomaly of the tricuspid valve. *Circulation.* 1959;19:165-187.
7. Genton E, Blount SG. The spectrum of Ebstein's anomaly. *Am Heart J.* 1967;73:395-425.
8. Anderson KR, Zuberbehler JR, Anderson RH, Becker AE, Lie JT. Morphologic spectrum of Ebstein's anomaly of the heart: a review. *Mayo Clin Proc.* 1979;54:174-180.
9. Schiebler GL, VanMierop LHS. Ebstein anomaly. In: Bergsma D, ed. *Birth Defects Compendium.* 2nd ed. New York, NY: Alan R Liss Inc; 1979:379-380.
10. VanMierop L, Schiebler G, Victoria B. Ebstein's anomaly. In: Adams FH, Emmanouilides GC, eds. *Heart Disease in Infants, Children and Adolescents.* 3rd ed. Baltimore, Md: Williams & Wilkins; 1983:283-296.
11. Sherman FE: *An Atlas of Congenital Heart Disease.* Philadelphia, Pa: Lea & Febiger; 1963.
12. Zuberbuhler JR, Allwork SP, Anderson RH. The spectrum of Ebstein's anomaly of the tricuspid valve. *J Thorac Cardiovasc Surg.* 1979;77:202-211.
13. Anderson RH, Shinebourne EA, Macartney FJ, Tynan M, eds. *Paediatric Cardiology.* New York, NY: Churchill Livingstone Inc; 1987;2.
14. Taussig H: *Congenital Malformations of the Heart.* 2nd ed. Cambridge, Mass: Harvard University Press; 1960;2.
15. Thieffry S, Aicardi J. Les spasmes en flexion du nourrisson étude clinique. *Sem Hop Paris.* 1958;34:1167-1178.
16. Aicardi J, Lefebvre J, Lerique-Loechlin A. A new syndrome: spasm in flexion, callosal agenesis, ocular abnormalities. *Electroencephalogr Clin Neurophysiol Suppl.* 1965;19:609-610.
17. Aicardi J, Chevrie JJ, Rousselie F: Le syndrome spasmes en flexion, agénesie calleuse, anomalies chorio-rétiennes. *Arch Fr Pediatr.* 1969; 26:1103-1120.
18. Engle MA, Payne TPB, Bruins C, Taussig HB. Ebstein's anomaly of the tricuspid valve: report of three cases and analysis of clinical syndrome. *Circulation.* 1950;1:1246-1260.
19. Anderson KR, Lie JT. Pathologic anatomy of the Ebstein's anomaly of the heart revisited. *Am J Cardiol.* 1978;41:739-745.
20. Nora JJ, Nora AH, Toews WH. Lithium, Ebstein's anomaly, and other congenital heart defects. *Lancet.* 1974;2:594-595.
21. Weinstein MR. Lithium teratogenesis. In: Cooper TB, Gershon S, Kline NS, Schou M, eds. *Lithium, Controversies and Unresolved Issues.* Princeton, NJ: Excerpta Medica; 1979:432-446.
22. Szabo KT. Teratogenic effect of lithium carbonate in the foetal mouse. *Nature.* 1970;225:73-75.
23. Wright TL, Hoffman LH, Davies J. Teratogenic effects of lithium in rats. *Teratology.* 1971;4:151-156.
24. Gralla EJ, McIlhenny HM. Studies in pregnant rats, rabbits and monkeys with lithium carbonate. *Toxicol Appl Pharmacol.* 1972;21:428-433.
25. Smithberg M, Dixit PK. Teratogenic effects of lithium in mice. *Teratology.* 1982;26:239-246.
26. Schülter G. Zur Wirkung von Lithium carmin und Lithium carbonate auf die Embryonalentwicklung der Maus. *Naunyn Schmiedebergs Arch Pharmacol.* 1971;270:56-64.
27. Jurand A. Teratogenic activity of lithium carbonate: an experimental update. *Teratology.* 1988;38:101-111.
28. Ullrich K, Böhm N. Early embryonal maldevelopment of the umbilical cord with defect of the abdominal wall and severe body malformations (dysplasia umbilico-fetalis). *Beitr Pathol.* 1977; 160:286-297.
29. Barr M, Heidelberger KP. Short umbilical cord: cause or effect of fetal anomalies? *Proc Greenwood Genetic Center.* 1983;2:100-101.
30. Grange DK, Arya S, Opitz JM, Laxova R, Herrmann J, Gilbert EF. The short umbilical cord. *Birth Defects.* 1987;23:191-214.
31. Donegan CC, Moore MM, Wiley TM Jr, Hernandez FA, Green JR Jr, Schiebler GL. Familial Ebstein's anomaly of the tricuspid valve. *Am Heart J.* 1968;75:375-379.
32. Davido A, Maarek M, Jullien JL, Corone P. Ebstein's disease associated with Fallot's tetralogy: apropos of a familial case, review of the literature, embryologic and genetic implications. *Arch Mal Coeur.* 1985;78:752-756.
33. Odgers PNB. The development of the atrioventricular valves in man. *J Anat.* 1938-1939; 73:643-647.
34. Perloff JK: *The Clinical Recognition of Congenital Heart Disease.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1987.

Video*Demonstration*
Video*Instruction*
Video*Enactment*

The AMA Video Clinic library of videotapes can expand your understanding with the latest on the diagnosis and treatment of more than 40 medical conditions.

AMA Video Clinic programs are produced in exciting, informative formats. Leading national experts will guide you through actual and simulated clinical procedures, role plays, demonstrations, interviews and more.

Find out more. Call 1-800-621-8335. In Illinois call collect 312-645-4987.

AMA *Video Clinic*

Expand your art by expanding your science.

HOUSE BASED PEDIATRICIANS (HBPs)

Huntington Memorial Hospital of Pasadena, California, a major affiliate of the University of Southern California School of Medicine, is seeking to hire four board eligible/certified pediatricians by July 1, 1989 to cover its 34-bed pediatric floor. These four house-based pediatricians (HBPs) will provide in-house coverage that traditionally would have been provided by pediatric interns or residents.

Founded in 1892, Huntington Memorial Hospital is a 606-bed non-profit medical center that serves the communities of the San Gabriel Valley of Los Angeles County. The total service area population of the San Gabriel Valley is approximately two million people. The Hospital offers a tertiary Infertility Center, Perinatal High-Risk Unit, a Neonatal ICU and renowned ECMO Center, a comprehensive Pediatric Center and a Pediatric ICU.

The compensation is competitive with the HMOs or other salaried positions in the area: $70,000 annual salary; health insurance (medical, dental, vision); life insurance ($50,000 term life); accidental death & dismemberment ($50,000); paid 3-week vacation; and a $1000 annual CME fund.

Those interested should send their CV and inquiries to Edgardo L. Arcinue, M.D., Head, Department of Pediatrics, 100 Congress Street, Pasadena, CA 91105; (818) 397-8688.

Are you
a **Pediatrician**
ready for
independent practice
with group advantages?
office partner
call coverage
referrals
support while building
teaching opportunities

REGIONAL
PERINATAL CENTER
1 1/2 hours from Chicago

Call Jo Grimm
(800) 638-6942

INSULIN IS NOT A CURE FOR DIABETES. IT JUST KEEPS PEOPLE ALIVE UNTIL WE FIND ONE.

Support the Research of the American Diabetes Association

American Diabetes Association®

CEJKA IS NOT A SWEDISH GAME SHOW

But you may have heard of us. For nearly ten years, Cejka (CHECK'-A) & Company has been retained by clients nationwide for thoughtful and thorough physician search.

Several PEDIATRIC searches are now in progress exclusively through Cejka for practices in:

VIRGINIA	TEXAS
ILLINOIS	MISSOURI
OKLAHOMA	NEVADA
INDIANA	LOUISIANA

GET TO KNOW US

Inquiries are confidential, and all fees/ expenses are paid by our clients. Call:

Julie Woolsey
CEJKA & COMPANY
222 South Central
St. Louis, MO 63105
1-800-365-2237

ACADEMIC PEDIATRIC ONCOLOGIST

The Department of Pediatrics, University of New Mexico School of Medicine, is seeking a BC/BE pediatric oncologist to join an active division of pediatric oncology to share clinical, teaching and research responsibilities. Excellent research opportunities for collaboration with our Cancer Center exist. This is a tenure-line position at the assistant/associate professor level.

Send letters of inquiry and CV to: John D. Johnson, M.D., Chairman, Pediatrics, University of New Mexico School of Medicine, Albuquerque, NM 87131 (phone 505-277-5551).

STREP TEST™
SHEEP BLOOD AGAR PLATES
LABORATORY CULTURE MATERIALS

- BACITRACIN DISKS
- URI-DIP®
  URINE CULTURE MATERIALS
- DELUXE INCUBATORS
- DISPENSERS
- INNOCULATING LOOPS
- SWABS

AVAILABLE FROM:

UNIVERSAL BIOLOGICAL LABS
DIAGNOSTIC DIVISION OF:
NATIONAL BIOLOGICAL CORPORATION

1532 ENTERPRISE PARKWAY
TWINSBURG, OHIO 44087
(216) 425-8180
OUTSIDE OHIO: 1-800-338-5045
IN OHIO: 1-800-227-6294

ORDER TODAY
FOR IMMEDIATE DELIVERY

INDEX TO ADVERTISERS

Allen & Hanburys, Division of Glaxo, Inc. 572A-D, 573
ARAMCO 604
Aurora Pediatric Clinic, S.C. 536
Burroughs Wellcome Company 535-536
Cejka & Company 574
Christie Clinic Association 524
CIGNA 528
Connaught Laboratories, Inc. 564-566
Fisons Corporation 515, 593-594
Grandview Hospital 524
Hamad Medical Corporation 524
Huntington Memorial Hospital 573
ICN Pharmaceuticals, Inc. 524A-D
McNeil Consumer Products Company ..... Cover 3
Mead Johnson Nutritional Division ..... Cover 2
Mennen Company 510
MSCI 573
National Biological Corporation 574
National Institutes of Health 515, 528
New Hanover Memorial Hospital 524
Rorer Pharmaceuticals 527-528
Ross Laboratories 513
Sandoz Pharmaceuticals 603-604
University of New Mexico 574
Wenatchee Valley Clinic 536
Wyeth-Ayerst Laboratories ..... Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia, Pa
Harold Levine, MPA, Galveston, Tex
Barbara Starfield, MD, Baltimore, Md
Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*How often have you found that the student to whom you gave glowing clinical evaluations was later found to be not so glowing? Do we have a consistent, fair, and objective means of assessing clinical problem solving that avoids the halo effect? Schwartz describes a computer problem-solving simulation and reports results of its use. See what you think of this tool.*—H.D.A.

Documentation of Students' Clinical Reasoning Using a Computer Simulation

William Schwartz, MD

• Computer simulations can provide both a clinical experience for teaching problem solving and a method of documenting a student's clinical reasoning style. The CAMPS simulation consists of approximately 500 items describing a patient's history, physical examination and laboratory results, and treatments. The student has full option to select any item in any order, producing a wide variation of performances. Since all of the students interact with the same clinical problems, the faculty member can make comparisons of that individual student with the class. From the record of the simulation encounter, the person responsible for student evaluations can prepare a narrative that lists the overall performance, the specific omissions and commissions, and comparisons with the class. Experience with a group of 111 students in a basic pediatric course showed that this method of documenting clinical inquiry detected a variety of levels of performances. Comparisons of the results of these tests with the faculty observations showed that 16% of these students who were judged to be very good or excellent in problem solving by the faculty performed at least 1 SD below the class average on the simulations. This project highlights the power of computer simulations to provide documentation of student performance with the additional benefit of a cost of less than $1 per student.

(*AJDC* 1989;143:575-579)

Computer simulations, increasingly used in teaching programs, can help the faculty document and evaluate students' clinical reasoning skills. In the teaching mode, the faculty uses these electronic patients to present common problems, to round out the clinical experience by allowing students to interact with patients not available in the clinics or hospital, or to demonstrate approaches to clinical problems. The student is given a clinical problem, then selects items from the history, physical examination, laboratory test, and treatment menus. The student has full control to select any item in any order with the goal of establishing a diagnosis and beginning treatment. At the end of the interaction, the student is informed that the diagnosis is correct or incorrect, told the cost of the assessment, and given a brief synopsis of the case. The student is then given a score that is a comparison of his or her approach with that of a faculty panel. Information about the score, cost, and all choices are saved in a student file.

When the focus changes from teaching to evaluation, the system becomes a source of information about clinical reasoning. The evaluator can review the record of choices to construct a summary of the student's approach to the problem, emphasizing any aspect of the process that fits the course's objectives, such as directness of the approach vs comprehensiveness, omission or commission errors, or cost factors. The following discussion details the development of a documentation system of student clinical reasoning skills using a computer-based patient simulation.

BACKGROUND

In the traditional system of assessing students after their four-week clerkship in pediatrics, the teaching attending physician, who observed students for at least 20 hours, wrote a narrative about the students' clinical skills. The areas included case presentations, medical knowledge, problem solving, participation in conferences and rounds, and interaction with patients. The house staff added comments about the student's clinical performance in patient care and their work with the hospital staff. Al-

Accepted for publication Nov 17, 1988.

From the University of Pennsylvania School of Medicine, Philadelphia, and The Children's Hospital of Philadelphia.

Reprint requests to The Children's Hospital of Philadelphia, Philaldelphia, PA 19104 (Dr Schwartz).

though there were criteria for each grade level, wide variations existed among individual evaluators, who frequently developed their own standards and emphasis to determine the final grades. The faculty checked descriptions on a scale of 1 to 5 and assigned an overall grade ranging from honors to failure.

A committee assigned to study the evaluation process requested more objectivity in the grading of problem solving and proposed the incorporation of computerized simulations into the assessment system. Their concerns mirrored the recent survey of pediatric student educators who expressed a need for an organized student evaluation.[1] The committee established the following guidelines for determining if the computer simulation can be incorporated into the evaluation system: (1) the process that the student used to solve problems needed to be documented; (2) administration and scoring of the test should be accomplished in an efficient manner; and (3) the test should not add excessive costs to the training programs.

```
NAME:-------          CLASS; STUDENT
SCORE: 61             COST:$505  DX: YES
laboratory  point value distribution:
-10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0  1  2  3  4  5  6  7  8  9  10
-------------------------------------------------------------------
  0  0  0  0  0  1  0  0  0  1  0  0  0  1  0  0  0  0  0  0
treatment value distribution
   Necessary    Unnecessary  Harmful
      0            2            0
History: 25    Physical  14   Consult 1
elapsed time:23
This person chose:  * PARTIAL LISTING FOR
                    THIS EXAMPLE**
        Appearance
        History
             HPI
               Duration
               what made it better
               What made it worse
             CNS
               trauma
               History of seizures
        LABORATORY  * COMPLETE LISTING*
            AMMONIA
            BLOOD CULTURE
            CHEMISTRY PANEL
            CBC
            CT HEAD
        TREATMENT
            PHENOBARBITAL
```

Fig 1.—Sample printout of student record. Narrative statement for student file is created from this record.

STUDENT POPULATION AND MATERIALS

Using cases developed from the CAMPS system (Dacis Software, Philadelphia),[2] the students interacted with the clinical problems during the four-week course and final examination. In this project, 111 students each took two additional cases as part of their final assessment. The diagnoses, costs, scores, and choice list, which were saved in student files, were printed and entered into special programs that aided in the analyses. Observations made from these records constitute the basis of this report.

The score given for the interaction requires some explanation. The scoring system is generated in two steps. First, the author of the case assigns values from −10 to +10 to laboratory tests depending on the utility, cost, and potential value or harm to the patient. Treatments are categorized as harmful, unnecessary, or necessary. The second phase consists of a panel of five faculty members who independently interact with the case. The program averages their choices to set the reference standard. For example, if three faculty members order a chest roentgenogram and two do not, the reference panel includes a chest roentgenogram as part of the idealized workup. Seven subscores (history, physical examination, laboratory test, treatment, consultation, cost, and diagnosis) contribute to the final score. The student's interaction is compared with the evaluations of the expert panel, producing a final grade that is a ratio of the student's seven subscores to the faculty's scores.

DEVELOPMENT OF THE DOCUMENTATION SYSTEM

The development of the documentation system involves a four-step process: recording the core information, adding details about specific points, comparison with the class, and making suggestions for improvement.

Step 1: Basic Information

A utility of the CAMPS system prints out the summary of the student record (Fig 1). This listing provides the basic information for the narrative summary: the student name, score, point value of laboratory tests, number of history and physical examination items, treatments, consultations, and diagnosis.

Step 2: Additional Details

This step moves from the quantitative evaluation to a qualitative one. The faculty member can not only see how many history items were selected but can check for important omissions and commissions. During the case creation, the faculty member can highlight questions that are critical in the assessment of the problem, in both making the diagnosis and ruling out important differential diagnoses. From a comparison of the student's choices with the list of important items, the evaluator can write a paragraph to highlight the omissions and commissions. In a newer version of this simulation, the computer will check to see how many of the important items were selected and create the report.

Step 3: Comparison With Other Students

Since all students interact with the same simulation, faculty can make comparisons among students' performances and incorporate them into the summary. These comparisons are especially helpful in showing the student who had a low

score how his or her performance differed from those of the majority of the class and the faculty panel. These differences are usually not in making the right diagnosis but rather in the detail of the history and the magnitude of the laboratory assessment.

The class data, when placed in a data manager program such as the REFLEX system (Borland International) and displayed in a scatter graph, show how the student performed in relationship with the class. A special feature of this system allows the display of both the student record and the graph with the individual highlighted by the cursor (Fig 2). For example, the records of the class can be entered into the database system. A graph is developed plotting the cost of the assessment against the number of important history questions. The screen is split to show records as well as the graph. The instructor can then move to a specific student by selecting the name or can move the cursor to a point on the graph and see the record that produced it. Showing this information to a student who has performed below the class average may help improve the evaluation by demonstrating the student's relationship with the class.

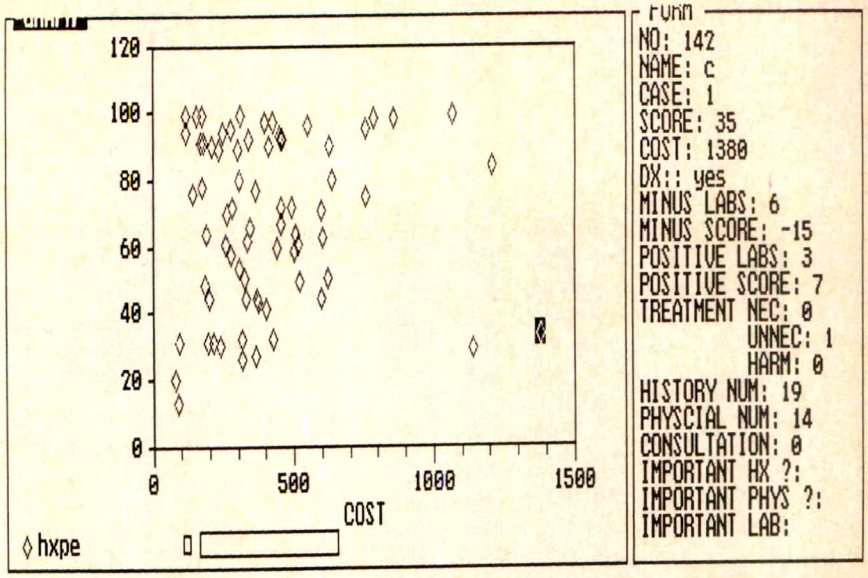


Fig 2.—Display of comparison of entire class comparing cost of evaluation with number of history and physical examination items selected. With the REFLEX system, an individual record can be displayed by highlighting a point on the graph (dark box in lower right portion).

Step 4: Making Suggestions for Improvement

The summary can end with a list of suggestions for improvement, for example, expand the differential diagnosis, focus or expand the history or physical examination, use the history rather than the laboratory tests to rule out diseases in the differential diagnosis, avoid ordering tests that measure the same function, and avoid overtreatment or undertreatment or use of too many consultants.

CONSTRUCTION OF THE NARRATIVE EVALUATION

From this evolution of information acquisition, starting with the summary of performance, adding details and comparisons with other students, a narrative evaluation can be constructed either by the faculty or by a special computer program. Using the case summary in Fig 1, the following paragraph can be created:

In this test of problem-solving skills, _____ scored a 61, below the class average, incurred a cost of $505, above the class average, on a case of seizures secondary to *Shigella* infection. He elicited a limited history that requested information about seizures, trauma, and medication but not a more comprehensive view of the problems of seizures in a febrile patient. He performed a complete neurologic examination but omitted the rest of the physical examination looking for causes of the fever. Problems in the laboratory section contributed to the major defect in his performance. He ordered an ammonia level measurement and computed tomogram of the head, a complete blood cell count, and a chemistry panel, but omitted important tests for a seizure in a febrile patient, such as a urine and stool culture as well as a lumbar puncture. He did make the right diagnosis but it was derived from inadequate information. His treatment with phenobarbital did not correspond to the diagnosis.

When compared with the other students in the group, _____ was in the group who asked the fewest questions. He ordered many tests with low or negative values. The costs of his assessment on these two cases were the highest in the class.

_____ would improve his performance by including more developmental history questions to determine if the child had any developmental delay that could be the basis for seizures, by considering infectious problems as the cause of the seizure, by eliciting information about environmental situations such as lead poisoning, by widening the scope of the laboratory tests to test for the common causes of seizures in a 1-year-old child, including glucose for hypoglycemic states, calcium, lead level, cultures, toxic screen, and drug screen. The ordering of a computed tomographic scan is considered important by many people but not as the initial test for the evaluation of a patient with these presenting symptoms.

COMPARISON WITH THE FACULTY OBSERVATIONS

Comparison between the information from the simulation and the impressions of student competencies recorded by the faculty points out the helpfulness of documentation of performance. Many faculty members feel better when they interact with the students and then determine the grade. Usually, these observations are not standardized and involve students working with a variety of patients rather than with a set of simulations. Other influences such as communication skills and personality may influence the evaluation. A comparison was made between the scores from the simulation and the faculty impressions about students' problem solving. Table 1 shows the faculty and computer simulation grades. Five students who received honors from the teaching attending physician scored less than 1 SD below the class mean in the simulation. These students tended to order too many laboratory tests, ruling out many diseases of very low frequency or adding to the cost by ordering expensive tests that the faculty panel did not se-

lect. Because their problem-solving approach differed markedly from those of both the faculty and their classmates, they should not be in the "honors" category, which for problem solving was defined as "comprehensive history and physical, identified problem, focused questions, clearly outlined appropriate treatment." At the other end of the scale, three students, who were graded in the "pass" category by the faculty but scored at the highest level in the simulations, could be helped by this documentation of their clinical reasoning. In trying to reconcile the divergent grades, the computer system presents documentation of performance and class comparisons, while the faculty members usually can give impressions with few examples to substantiate their grade.

ADVANTAGES OF THE SYSTEM

Use of simulations provides documentation of how a student integrates medical knowledge in evaluating a problem. Knowing what questions were asked and which laboratory tests were ordered gives the faculty insights into the student's thought process. Working from a common data source enables the reviewer to make comparisons among all students in the class. Without this simulation, the review of a student writeup of a patient focuses on organization of information, completeness of history, and writing style, since the faculty member has usually not seen the patient. In this exercise, the reviewer "knows the patient" and uses this knowledge to better critique the exercise.

The latitude in the system design allows the student the opportunity to choose the items in any order, producing a wide range of pathways to make the diagnoses. Table 2 shows the class averages and SDs of three subscores (final score, cost of evaluation, and number of history choices) on three cases. The wide range of scores (24 to 98) shows that the students accumulate a variable amount of information to reach the diagnosis. The number of history items selected ranged from four to 58 in case 1. Since most students make the

Table 1.—Comparison of Faculty Grade With Computer Score

	Faculty Grade, No.	Computer Test, No.			
		Honor	High Pass	Pass	Fail
Honor	30	4	21	4	1
High pass	55	10	34	9	2
Pass	26	3	18	3	2

Table 2.—Summary of Class Performance on Final Score and Two Subscores of the Simulated Case Exercise

	Case 1	Case 2	Case 3
Score			
Mean	73	69	73
High	98	94	94
Low	24	20	40
SD	16	13	13
Cost, dollars			
Mean	408	407	269
High	1380	1813	1416
Low	265	259	209
SD	265	259	209
History items			
Mean	38	33	34
High	58	55	63
Low	4	6	10
SD	15	14	14

Table 3.—Representation of a Final Score Report Showing Diverse Performance in Number of Choices and Cost of Evaluation

Student No.	Grade, %	Diagnosis Correct	Cost, Dollars	Items Selected, No.			Laboratory Value, Points*	No. of Consultations
				History	Physical Examination	Laboratory Tests		
1	53	Yes	175	21	19	5	0	0
2	66	Yes	908	23	13	13	5	4
3	69	Yes	173	26	11	5	0	0
4	76	Yes	75	37	26	1	−1	0
5	78	Yes	713	33	34	5	5	2
6	79	Yes	178	52	39	5	6	0
7	81	Yes	228	47	32	3	5	1
8	86	Yes	613	52	39	6	12	1
9	90	Yes	576	47	34	5	11	0
10	91	Yes	773	52	39	7	16	. . .
Average	77	. . .	441	39	29	7	5	1

*The sum of all positive and negative laboratory values.

correct diagnosis, the majority of the variance in the final score comes from the history, laboratory score, and cost. The cost of the evaluation ranged from $265 to $1380, reflecting the number and kinds of laboratory tests, consultations, and treatments.

The system helps the instructors look beyond the skill of making the correct diagnosis and helps identify those students who have clinical reasoning styles that may lead to continued problems if not corrected. Table 3 demonstrates that within a group of ten students who made the correct diagnosis, the final scores vary in a wide range, highlighting the contribution of the other subscores. Student 2, with a score of 66, the second lowest score in the group, shows how this system can screen for problem performances and give an indication of the basis of the low score. The cost of the evaluation was the highest because most laboratory tests were ordered (13) with low laboratory value score (the sum of all positive and negative laboratory test results), indicating the selection of many unnecessary tests. The ordering of four consultations contrasted with the 60% of the class with higher scores who did not ask for one consultation. This performance of student 2 justifies the comment that "clinical reasoning skills were below class average because of incomplete history and physical examination, selection of unimportant laboratory tests, and overuse of consultants." By pointing out specific examples of overinvestigation or underinvestigation and inappropriate use of information, the faculty can help students develop insight into their assessment problems. The instructor can follow up the initial student evaluation by asking the student to evaluate additional cases and providing the documentation of the changes in clinical reasoning style.

The electronic grading and system utilities for retrieval allow rapid accumulation of the information for review of the students. This time-saving effort helps to improve the system at no additional expense. This organized method of observation also helps screen the class for students with difficulty in the clinical reasoning area. Analyses of costs show that for a class of 150 students, the development and usage expenses are about 50 cents per student over a two-year period.

LIMITATIONS

This system documents clinical reasoning but does not provide enough information to claim the power to evaluate problem solving. McGuire[3] recently critiqued the literature highlighting the problem of definition of problem solving and the difficulty of making generalizations from the results of one case to other cases. Unlike psychological testing, where a new test can be compared with an accepted standard, problem solving has no such reference test. This report sidesteps this problem by not claiming the power to define the students' problem solving or clinical reasoning skills, but rather documenting and assessing data acquisition. Some preliminary work indicates that the CAMPS final score does measure skills associated with the problem-solving process. In a previous study, using psychological tests designed to evaluate problem-solving skills, Diserens et al[2] showed that CAMPS tested medical problem-solving skills, distinct from general problem solving as measured by locus-of-control and ground-embedded figures tests. This study also demonstrated that the final score in difficult cases discriminated between the performance of experienced physicians and students. In easier cases, the faculty scored higher than students but not at a significant level. They estimated that nine cases should be used to ensure that the test was a valid measurement of problem solving.

The use of more than two cases would be ideal, but because the cases were part of the total evaluation package, more time could not be allotted for the simulations. The results of the clinical reasoning aspect of the examination, when combined with the other aspects of the evaluation program, clinical work, presentations, and multiple-choice examinations, enriches the information for both the written evaluation and discussions with the students. The additional information about problem solving is generated by the student and computer, allowing the faculty to focus on other evaluation activities.

Many students are concerned about the completeness of their evaluation. Should they make the diagnosis with the minimum of inquiries or should they rule out some important differential diagnoses? This scoring system follows the faculty approach, which is usually a compromise between the two extremes. Should the student who elicits a brief history and orders several tests that confirm the diagnosis be penalized with a low score since he or she got the right answer but did not follow the faculty's approach? This scoring system looks for how the student solves the problem, which requires ruling out certain differential diagnoses as well as making the correct one. In some cases, the faculty does take this direct route since the case is either classic or too easy. If the goal of the course is to make the fewest choices to get to the answer, then the expert panel could act in that mode. In general, the majority of the students score about 80, indicating that they take the general approach of the faculty.

Another generic question centers on the problem of how closely the work on simulations reflects what the student would do when working with patients. Few studies have addressed this problem. Goran et al[4] compared performances on a patient management problem (PMP) with records from actual clinical encounters of patients with urinary tract infections. They concluded that the history was more complete and more urine cultures were ordered for the PMP than for the patient. This study, limited to one problem, indicates that there is a difference in how some students act between a test and a clinical setting. Page and Fielding[5] reported similar observations about better performance on PMP than in a real setting.

These limitations should not negate the documentation provided by the system but rather should present a caution of not overinterpreting the results.

References

1. Sahler OJZ, Lysaught JP, Greenberg LW, et al: A survey of undergraduate pediatric education: Progress in the 1980s. *AJDC* 1988;142:519-523.
2. Diserens D, Schwartz W, Guenin M: Measuring the problem solving ability of students and residents by microcomputer. *J Med Educ* 1986;61:461.
3. McGuire CH: Medical problem-solving: A critique of the literature. *J Med Educ* 1985;60:587-595.
4. Goran MJ, Williamson JW, Gonnella JS: The validity of patient management problems. *J Med Educ* 1973;48:171.
5. Page GG, Fielding DW: Performance on PMP's and performance in practice: Are they related? *J Med Educ* 1980;55:529.

Neonatal *Staphylococcus epidermidis* Meningitis With Unremarkable CSF Examination Results

Jeffrey Gruskay, MD; Mary Catherine Harris, MD; Andrew T. Costarino, MD; Richard A. Polin, MD; Stephen Baumgart, MD

• We identified 10 infants (mean ± SD birth weight, 1000 ± 500 g; gestation, 29 ± 3 weeks; postnatal age, 24 ± 19 days) who had *Staphylococcus epidermidis* meningitis despite unremarkable cerebrospinal fluid (CSF) blood cell counts and glucose and protein levels. *Staphylococcus epidermidis* meningitis was diagnosed if all the following criteria were satisfied: (1) a CSF culture positive for *S epidermidis* within 48 hours, (2) a blood culture positive for *S epidermidis* with antibiotic sensitivities identical to those of the CSF isolate, and (3) clinical symptomatology. Lumbar puncture yielded white blood cell counts lower than 10×10^6/L in 8 infants. Two subjects had CSF white blood cell counts of 11×10^6/L and 14×10^6/L. Cerebrospinal fluid glucose (2.8 ± 0.9 mmol/L) and protein (1.15 ± 0.32 g/L) concentrations were also unremarkable. Infants were treated with parenteral antibiotics for 19 ± 5 days. There was no mortality or short-term morbidity. *Staphylococcus epidermidis* is a recognized cause of nosocomial meningitis in low-birth-weight infants and frequently occurs without CSF abnormalities.

(*AJDC.* 1989;143:580-582)

Staphylococcus epidermidis is currently the most common pathogen associated with hospital-acquired infection in many neonatal intensive care units.[1-3] In the past, most cases of *S epidermidis* bacteremia were associated with the placement of foreign bodies, such as vascular catheters or chest tubes.[4] Similarly, cerebrospinal fluid (CSF) infections with *S epidermidis* were most frequently reported in patients with intraventricular catheters, eg, ventriculoperitoneal or ventriculojugular shunts for hydocephalus.[5,6] Recently, however, investigators have reported *S epidermidis* infections in the absence of foreign bodies, including systemic sepsis, meningitis, and other focal infections (osteomyelitis, septic arthritis, enterocolitis, otitis media, pneumonia, and urinary tract infections).[7-10] The population at greatest risk is the chronically ill, very-low-birth-weight infant who requires prolonged hospitalization.

The diagnosis of bacterial meningitis is contingent on isolation of the infecting organism from a CSF culture.[11] Abnormalities of the CSF cell count and glucose and protein concentrations may provide corroborative evidence of CSF infection and are useful for the early diagnosis and presumptive treatment of suspected meningitis pending definitive culture results. However, central nervous system infection in the absence of CSF abnormality has occasionally been observed in older children[12-15] and, anecdotally, as a rare event in neonates.[16] We have observed *S epidermidis* meningitis presenting with absent or minimal CSF abnormalities in increasing frequency as nosocomial bacteremia with this organism becomes more common.

This report describes 10 infants with *S epidermidis* meningitis and unremarkable CSF examination findings. Both cellular and chemical parameters of this emerging clinical entity are described.

METHODS

We reviewed the medical records of all neonates admitted to our infant intensive care unit during a 2-year period who had CSF cultures positive for *S epidermidis* and unremarkable CSF examination findings. Infants were characterized for the following: clinical signs and symptoms, age of onset of meningitis, antimicrobial agents used to treat meningitis and duration of therapy, and morbidity and mortality during hospitalization. This study was performed in compliance with the guidelines concerning research in human subjects at The Children's Hospital of Philadelphia, Pa.

Both CSF and blood cultures were obtained using standard aseptic technique. Cerebrospinal fluid cultures were plated on blood and chocolate agar and in enriched eugonic broth, incubated at 35°C to 37°C, and examined for growth every 24 hours. Cultures were considered positive for *S epidermidis* if growth occurred on the agar plates within 48 hours of sampling. Staphylococci were identified as *S epidermidis* with the API-Staph Ident System, Analytab Products, New York, NY.[17] Antibiotic sensitivity patterns were obtained using disk diffusion methods.[18] Blood cultures were evaluated using identical criteria. Other cultures obtained during evaluation for meningitis and sepsis were also reviewed.

In the presence of unremarkable CSF examination results, the diagnosis of *S epidermidis* meningitis was made if *all* the following criteria were satisfied: (1) a CSF culture positive for *S epidermidis* within 48 hours of plating, (2) a blood culture positive for *S epidermidis* with an antibiotic sensitivity pattern identical to that of the CSF isolate, and (3) the presence of clinical signs or symptoms of systemic infection. For the purpose of this report, the CSF examination findings were considered unremarkable if the white blood cell count was less than 15×10^6/L, the protein concentration was less than 1.60 g/L,[19-21] and the glucose concentration was greater than 1.7 mmol/L.[22] These limit values correspond to published ranges for CSF results in premature infants with negative cultures past 2 weeks of age.[19-22]

Hematologic values obtained as part of the evaluation for infection were also reviewed. Abnormal values were defined as a white blood cell count greater than 20×10^9/L or less than 5×10^9/L,[23,24] a total neutrophil count less than 2×10^9/L, an immature to total neutrophil ratio greater than 0.12,[25] and a platelet count less than 150×10^9/L.[26]

Accepted for publication December 20, 1988.

From the Division of Neonatology, The Children's Hospital of Philadelphia, the Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia.

Reprint requests to Division of Neonatology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Baumgart).

RESULTS

Ten infants satisfied all criteria for the diagnosis of *S epidermidis* meningitis in the absence of significant CSF abnormalities. The clinical characteristics of the 10 study infants included a mean ± SD birth weight of 1000 ± 500 g and a gestational age of 29 ± 3 weeks (Table 1). The onset of signs and symptoms occurred at a mean of 24 days of life (range, 13 to 67 days) and included an increase in significant apnea with bradycardia in 8 infants, lethargy in 3, cardiovascular instability in 3, feeding intolerance in 3, and respiratory decompensation in 2 infants.

The results of the CSF cell and differential counts and chemical analyses for glucose and total protein concentrations in the study infants are also presented in Table 1. The mean CSF white blood cell count was 6×10^6/L (range, 0 to 14×10^6/L). Only two infants had counts greater than 10×10^6/L, with differential counts of 0.05 or fewer polymorphonuclear leukocytes. Cerebrospinal fluid glucose concentrations ranged from 1.8 to 5.0 mmol/L (mean, 2.8 mmol/L), and protein concentrations ranged from 0.75 to 1.77 g/L (mean, 1.15 g/L). An elevated protein value (1.77 g/L) was obtained from one infant following grade IV intraventricular hemorrhage that was unrelated to the onset of *S epidermidis* meningitis.

Other cultures positive for *S epidermidis* included the following: umbilical venous catheter tips (three infants), radial artery catheter tip (one infant), urine (one infant), wound (one infant), and stool (one infant). All isolates from a given individual had identical antibiotic sensitivity patterns.

The hematologic profiles of study infants are presented in Table 2. Seven infants had abnormal peripheral white blood cell counts suggestive of bacterial infection, and two were severely neutropenic. Two infants had significant thrombocytopenia.

The 10 infants with meningitis each received appropriate parenteral antimicrobial therapy for a range of 10 to 30 days. Seven of 10 infants received antibiotic therapy for 3 or more weeks as determined by their attending and house staff physicians. Due to antimicrobial resistance patterns, vancomycin hydrochloride was required to treat 9 of the 10 infants with meningitis. The remaining patient received vancomycin for 3 days pending sensitivity testing and was given oxacillin sodium for 7 days thereafter. There were no deaths related to *S epidermidis* meningitis and no episodes of hydrocephalus as a result of meningitis. Hydrocephalus developed in 1 infant secondary to an intraventricular hemorrhage and prior to the diagnosis of meningitis.

Table 1.—Characteristics of Patient Population and CSF* Measurements

Patient No.	Gestation, wk	Birth Weight, g	Age at Onset of Meningitis, d	CSF Measurements: White Blood Cell Count, $\times 10^6$/L	CSF Measurements: Glucose, mmol/L	CSF Measurements: Protein, g/L
1	23	540	16	9	3.0	0.92
2	30	550	16	14	2.1	1.48
3	28	700	21	0	3.3	1.18
4	28	850	54	1	3.2	0.75
5	26	910	15	8	1.8	1.77†
6	29	990	13	2	2.2	. . .
7	29	1020	14	1	2.4	1.11
8	31	1040	14	2	5.0	1.17
9	30	1170	67	11	2.7	0.81
10	34	2360	13	7	2.8	1.20
Mean (SD)	29 (3)	1000 (500)	24 (19)	6 (5)	2.8 (0.9)	1.15 (0.32)

*CSF indicates cerebrospinal fluid.
†This infant had an elevated CSF protein concentration and grade IV intraventricular hemorrhage.

Table 2.—Peripheral White Blood Cell Counts in Neonates With *Staphylococcus epidermidis* Meningitis

Patient No.	White Blood Cell Count, $\times 10^9$/L	Total Neutrophil Count, $\times 10^9$/L	Immature to Total Neutrophil Ratio	Platelet Count, $\times 10^9$/L
1	19.4	12.8	0.21*	191
2	3.1*	1.3*	0.00	47*
3	5.1	3.5	0.25*	119*
4	23.6*	15.8	0.12	174
5	16.8	6.0	0.03	418
6	13.5	7.3	0.02	296
7	11.1	4.6	0.15*	425
8	8.8	. . .	. . .	341
9	4.6*	1.5*	0.24*	150
10	22.6*	10.8	0.08	370

*These values are suggestive of infection.[23-26]

COMMENT

We describe 10 infants with *S epidermidis* meningitis who had unremarkable CSF white blood cell counts and glucose and protein concentrations. In every infant the diagnosis of *S epidermidis* meningitis was made using a CSF culture positive within 48 hours in combination with blood isolates that had identical antibiotic susceptibility patterns. Clinical signs and symptoms were compatible with meningitis in the newborn infant, and all infants were treated accordingly.

In previous studies, CSF infections with *S epidermidis* have been most frequently reported in patients with intraventricular catheters (ie, ventriculoperitoneal or ventriculojugular shunts for hydocephalus).[5,6] *Staphylococcus epidermidis* meningitis with CSF abnormalities has also been reported in the

absence of these appliances.[7,27,28] Noel and Edelson[7] indentified 23 infants with *S epidermidis* bacteremia, 2 of whom had positive CSF cultures. Baumgart et al[27] described 1 meningitic infant among 13 infants with *S epidermidis* bacteremia. Visser and Hall[28] reported on 8 infants with *S epidermidis* bacteremia, 2 of whom had positive CSF cultures. These studies are consistent with the presumed pathogenesis of neonatal meningitis as a sequela to bacteremia.[11]

Culture-proved meningitis without significant changes in the CSF has been described occasionally in children and rarely in neonates.[12-15,22,28] Sarff and colleagues[22] described 119 infants with meningitis, 1 of whom had a culture positive for *Escherichia coli* despite normal CSF findings. Visser and Hall[28] described 39 infants with meningitis, 6 of whom initially had normal CSF findings, including 1 with *S epidermidis* meningitis. Repeated lumbar punctures in 5 of these infants disclosed a characteristic pleocytosis and/or abnormal glucose and protein concentrations. To our knowledge, our study reports the first series of newborn infants with *S epidermidis* meningitis with unremarkable CSF findings. These findings suggest that meningeal infection with this organism may occur frequently in this population in the absence of early diagnositic CSF abnormalities.

The mechanism responsible for the minimal to absent CSF pleocytosis in *S epidermidis* meningitis is currently unknown. Possibilities include the young age of the patients,[29] the nature of the infecting microorganism,[30,31] and the timing of the lumbar puncture in relation to the stage of the disease.[31,32] Previous studies in adults have reported that meningeal infection with *S epidermidis* caused only minimal or no abnormalities of CSF white blood cell counts and chemistry findings.[30] Another study has correlated increased CSF white blood cell counts with high bacterial densities in both CSF and blood,[31] suggesting the possibility of low-density infection as the basis for minimal CSF change. Finally, this entity may simply represent the presence of blood-borne bacteria in the CSF, without inflammatory consequences. Future studies should address the relationship between the quantity of microorganisms and the number of leukocytes in the CSF of newborn infants with *S epidermidis* meningitis.

The results of the present study raise several issues concerning treatment of the neonate with *S epidermidis* meningitis and unremarkable initial CSF examination results. Once *S epidermidis* with identical antibiotic sensitivities is recovered from multiple systemic cultures, as in the present study, significant infection is highly suspect and should be treated accordingly. In the present study, the physicians treating these infants frequently prescribed prolonged parenteral antibiotic therapy, beyond the usual 7- to 10-day course recommended for sepsis. Moreover, in the future, repeated lumbar puncture may provide further information to confirm the diagnosis of meningitis with repeated CSF examinations and to evaluate antibiotic efficacy with repeated cultures. The risk of performing this procedure in the critically ill neonate, however, should be carefully considered.[33] Finally, follow-up of these infants should include screening for subtle sequelae of meningitis.

References

1. Placzek MM, Whitelaw A. Early and late neonatal septicemia. *Arch Dis Child.* 1983;58:728-731.
2. Anday EK, Talbot GH. Coagulase-negative staphylococcus bacteremia: a rising threat in the newborn infant. *Ann Clin Lab Sci.* 1985;15:246-251.
3. Battisti O, Mitchison R, Davies PA. Changing blood culture isolates in a referral neonatal intensive care unit. *Arch Dis Child.* 1981;56:775-778.
4. Fleer A, Senders R, Visser M, et al. Septicemia due to coagulase-negative staphylococcus in a neonatal intensive care unit: clinical and bacteriologic features and contaminated parenteral fluids as a source of sepsis. *Pediatr Infect Dis.* 1983;2:426-431.
5. Shurtleff DB, Foltz EL, Weeks RD, Loeser J. Therapy of *Staphylococcus epidermidis:* infections associated with cerebrospinal fluid shunts. *Pediatrics.* 1974;53:55-62.
6. Schoenbaum SC, Gardner P, Shillito J. Infections of cerebrospinal fluid shunts: epidemiology, clinical manifestations and therapy. *J Infect Dis.* 1975;131:543-552.
7. Noel GJ, Edelson PJ. *Staphylococcus epidermidis* bacteremia in neonates: further observations and the occurrence of focal infections. *Pediatrics.* 1984;74:832-837.
8. Scherer LR, West KW, Weber TR, Kleiman M, Grosfeld JL. *Staphylococcus epidermidis* sepsis in pediatric patients: clinical and therapeutic considerations. *J Pediatr Surg.* 1984;19:358-361.
9. Jordan PA, Iravani A, Richard GA, Baer H. Urinary tract infection caused by *Staphylococcus saprophyticus. J Infect Dis.* 1980;142:510-515.
10. Gruskay JA, Abbasi S, Anday E, Baumgart S, Gerdes J. *Staphylococcus epidermidis* associated enterocolitis. *J Pediatr.* 1986;109:520-524.
11. Klein JO, Marcy SM. Bacterial sepsis and meningitis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn.* Philadelphia, Pa: WB Saunders Co; 1983:679-735.
12. Moore CM, Ross M. Acute bacterial meningitis with absent or minimal cerebrospinal fluid abnormalities. *Clin Pediatr.* 1973;12:117-118.
13. Polk DB, Steele RW. Bacterial meningitis presenting with normal cerebrospinal fluid. *Pediatr Infect Dis J.* 1987;6:1040-1042.
14. Smales OR, Rutter N. Difficulties in diagnosing meningococcal meningitis in children. *Br Med J.* 1979;1:588.
15. Fishbein DB, Palmer OL, Porter KM, Reed WP. Bacterial meningitis in the absence of CSF pleocytosis. *Arch Intern Med.* 1981;141:1369-1372.
16. Fosson AR, Fine RN. Neonatal meningitis: presentation and discussion of 21 cases. *Clin Pediatr.* 1968;7:404-410.
17. Aldridge KE, Stratton CW, Patterson LS, et al. Comparison of the Staph-Ident System with a conventional method for species identification of urine and blood isolates of coagulase-negative staphylococci. *J Clin Microbiol.* 1983;17:516-520.
18. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests.* 3rd ed. Villanova, Pa: Villanova University Press, 1984.
19. Otila E. Studies on the cerebrospinal fluid in premature infants. *Acta Paediatr Scand.* 1948;35(suppl 8):1-100.
20. Gyllensward A, Malmstrom S. The cerebrospinal fluid in immature infants. *Acta Paediatr Scand.* 1962;135(suppl):54-62.
21. Klein JO, Feigin RD, McCracken GH. Report of the task force on diagnosis and management of meningitis. *Pediatrics.* 1987;78:959-982.
22. Sarff LD, Platt LH, McCracken GH. Cerebrospinal fluid evaluation in neonates: comparison of high-risk infants with and without meningitis. *J Pediatr.* 1976;88:473-477.
23. Philip AGS. Detection of neonatal sepsis of late onset. *JAMA.* 1982;247:489-492.
24. Philip AGS, Hewitt JR. Early diagnosis of neonatal sepsis. *Pediatrics.* 1980;65:1036-1041.
25. Manroe BL, Weinberg AG, Rosenfeld CR, Browne R. The neonatal blood count in health and disease: I. reference values for neutrophilic cells. *J Pediatr.* 1979;95:89-98.
26. Kuchler H, Fricker H, Gugler E. La formula sanguine dans le diagnostic precoce de la septicemia du nouveau. *Helv Pediatr Acta.* 1976;31:33-46.
27. Baumgart S, Hall SE, Campos JM, Polin RA. Sepsis with coagulase-negative staphylococci in critically ill newborns. *AJDC.* 1983;137:461-463.
28. Visser VE, Hall RT. Lumbar puncture in the evaluation of suspected neonatal sepsis. *J Pediatr.* 1980;96:1063-1067.
29. Michael M, Barrett DJ, Mehta P. Infants with meningitis without cerebrospinal fluid pleocytosis. *AJDC.* 1986;140:851.
30. Olson DA, Hoeprich PD. Analysis of bacterial isolates from cerebrospinal fluid. *J Clin Microbiol.* 1984;19:144-146.
31. LaScolea LJ, Dryja D. Quantitation of bacteria in cerebrospinal fluid and blood of child with meningitis and its diagnostic significance. *J Clin Microbiol.* 1984;19:187-190.
32. Onorato IM, Wormser GP, Nicholas P. 'Normal' CSF in bacterial meningitis. *JAMA.* 1980;244:1469-1471.
33. Harris MC, Polin RA. Neonatal septicemia. *Pediatr Clin North Am.* 1983;30:243-258.

Prenatal Cocaine Exposure Is Associated With Respiratory Pattern Abnormalities

Ira J. Chasnoff, MD; Carl E. Hunt, MD; Ron Kletter, PhD; David Kaplan, MD

• As retrospectively determined, the rate of sudden infant death syndrome in 66 infants prenatally exposed to cocaine was 15%, compared with only 4% among infants exposed to opiates. This prospective evaluation of cardiorespiratory pattern in 32 cocaine-exposed and 18 methadone-exposed infants was therefore performed to further evaluate the effects of intrauterine exposure. The two groups were similar in maternal age, race, and cigarette, alcohol, and marijuana use and in gestational age, sex, and birth weight. Apnea density and episodes of periodic breathing exceeded the 95th percentile for normal infants in 12 (38%) of 32 of cocaine-exposed infants vs only 1 (6%) of 18 opiate-exposed infants. Five cocaine-exposed but no opiate-exposed infants had apnea of infancy, and all 5 of these infants had an abnormal cardiorespiratory pattern. In all 13 infants with an abnormal cardiorespiratory pattern, theophylline treatment resulted in normalization of the respiratory pattern and was associated with absence of any (further) clinical events. In summary, infants prenatally exposed to cocaine have a higher incidence of cardiorespiratory pattern abnormalities than do infants with methadone or no prenatal drug exposure.

(*AJDC*. 1989;143:583-587)

Several infant groups are thought to be at increased risk for sudden infant death syndrome (SIDS), among them infants born to narcotic-addicted women.[1,2] At the Perinatal Center for Chemical Dependence at Northwestern University Medical School, Chicago, Ill, we have observed a rate of SIDS of 4% among infants delivered to narcotic-addicted women. During the past several years, however, there has been a marked increase in the number of cocaine-using women seeking prenatal care and an apparent increase in the occurrence of SIDS. Among 56 infants born between 1980 and 1985 to cocaine-using women enrolled in the Family Addiction Center for Education and Treatment, San Francisco, Calif, and 10 infants born between 1980 and 1983 to cocaine-using women enrolled in the Perinatal Center for Chemical Dependence prior to the initiation of any SIDS intervention program, 10 of the 66 infants died of SIDS (8 of 56 from San Francisco and 2 of 10 from Chicago), an overall incidence of 15%. Autopsies on all 10 infants revealed no identifiable cause of death. Of these 10 infants (60% black), 8 were delivered at a gestational age of 37 weeks or more, 1 at 36 weeks, and 1 at 34 weeks. The mothers of 8 of the infants with SIDS had smoked cigarettes, and 3 had used alcohol in addition to cocaine. All 10 infants had at least mild irritability at birth, and 2 had been treated with paregoric in the first 2 weeks of life for neonatal abstinence. The mean age at death for the 10 infants was 6 weeks (range, 9 to 180 days). The overall rate of SIDS in Cook County, Illinois, during this same period was 0.27%, with a rate of 0.83% in all preterm infants.[3]

Due to this apparent high rate of SIDS in infants prenatally exposed to cocaine, this prospective study was performed to determine the incidence of cardiorespiratory pattern abnormalities in such infants. Our hypothesis was that infants born to cocaine-using women are at increased risk for cardiorespiratory pattern abnormalities.

METHODS

This prospective study of cocaine-exposed infants whose mothers were enrolled in the Perinatal Center for Chemical Dependence was initiated in 1984. Institutional Review Board approval was obtained for this drug-dependency clinical research program; informed consent was obtained prenatally for the prenatal components and (separately) for the postnatal components, the latter including the postdischarge pneumogram. Two groups of infants delivered at a gestational age of 38 weeks or more were enrolled. The first group consisted of 32 infants delivered over an 18-month period to all cocaine-using women who enrolled for obstetric care and for chemical dependence therapy at the Perinatal Center. Seventeen of the women used cocaine only in the first trimester of pregnancy, and the remaining women used cocaine throughout pregnancy. The second group consisted of 18 infants delivered during this same period to women addicted to heroin; these women were converted to low-dose methadone maintenance therapy during the first or second trimester. All women in both the cocaine and the narcotic groups received intensive obstetric and psychotherapeutic care during their pregnancies.[4,5]

The cocaine- and narcotic-addicted groups of women were similar in mean age (27.4 vs 28.2 years, respectively), gravidity (3.9 vs 4.2, respectively), and racial distribution: 15 black, 14 white, and 3 Hispanic in the cocaine group and 5 black, 10 white, and 3 Hispanic in the methadone group ($\chi^2 = 1.9$, not significant). Evaluation of substance abuse patterns (Table 1) was performed using urinary toxicologic studies that screened for drugs of use or abuse (ie, opiates, amphetamines, barbiturates, benzodiazepines, propoxyphene, cocaine, nicotine, marijuana, and phencyclidine). Among the two groups of women, mean consumption of alcohol (beer, wine, or hard liquor converted to absolute milliliters of alcohol per week) and use of cigarettes and marijuana were substantial but similar in the two groups. Eight of the cocaine-using women were concurrently addicted to heroin on presentation to the program and therefore began methadone maintenance therapy. Their mean daily methadone dose in the third trimester was similar to that required by the women in the narcotic group.

The 50 neonates were examined at birth; gestational age, weight, length, and head circumference were recorded. The cocaine-

Accepted for publication February 13, 1989.

From the Departments of Pediatrics (Drs Chasnoff and Hunt) and Psychiatry (Drs Chasnoff, Kletter, and Kaplan), Northwestern University Medical School, Chicago, Ill. Dr Hunt is now with the Department of Pediatrics, Medical College of Ohio, Toledo.

Presented in part to the Society for Pediatric Research, Washington, DC, May 8, 1986.

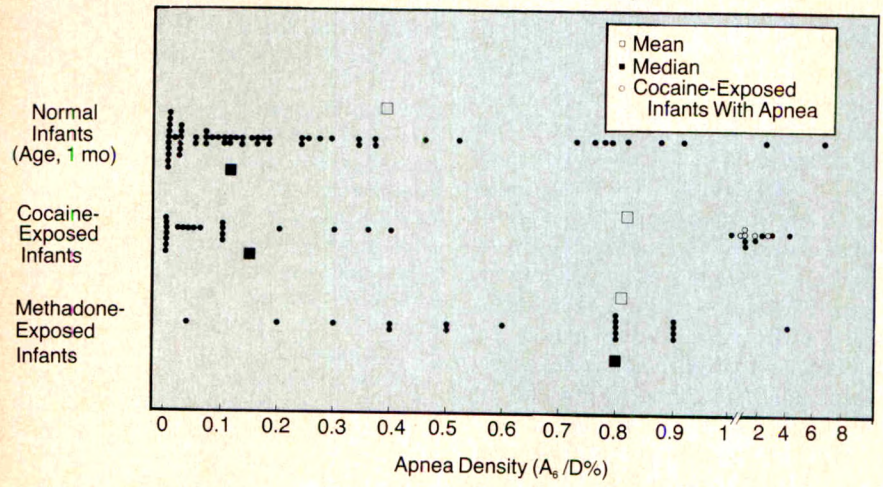
Reprint requests to Department of Pediatrics, Medical College of Ohio, PO Box 10008, Toledo, OH 43699-0008 (Dr Hunt).

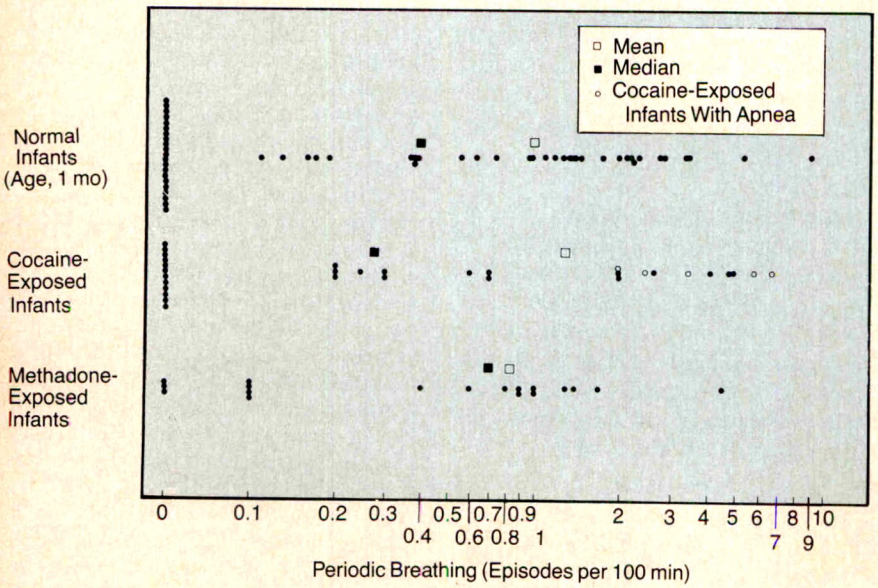
Table 1.—Substance Abuse Patterns During Pregnancy in 32 Women Using Cocaine and in 18 Women Using Methadone*

	Cocaine	Methadone
Alcohol, mL/wk	18.0 ± 10.4	27.0 ± 12.7
Cigarettes, No./d	11.2 ± 2.2	13.1 ± 3.6
Marijuana per mo	10.9 ± 4.4	16.1 ± 7.1
Methadone dose, mg	6.8 ± 3.4†	10.2 ± 2.4

*Values are expressed as mean ± SEM. For each item, the group differences are not statistically significant (ANOVA).
†In eight women taking methadone.

Comparison of individual respiratory pattern values in cocaine- and methadone-exposed infants with those in normal infants.[6] In the cocaine-exposed group, the five infants presenting for evaluation only after the occurrence of symptomatic apnea had statistically higher apnea density (defined as the total duration of all respiratory pauses of 6 seconds or more, expressed as percent of total sleep time [A_6/D%]) and periodic breathing (expressed as number of episodes per 100 minutes of total sleep time) values than did the remainder of the cocaine-exposed group ($P<.01$, Table 2). Top, The A_6/D% values are significantly greater in the cocaine-exposed infants than in the normal infants ($P<.05$). Bottom, Periodic breathing values.





and the narcotic-exposed neonates had similar mean birth weights (2960 vs 2980 g, respectively), lengths (49 cm for each group), and head circumferences (33 cm for each group). For all 50 neonates, urinary toxicologic studies were performed within the first 48 hours of birth. At 8 to 14 days of age, a two-channel, 24-hour outpatient cardiorespiratory recording[6,7] was obtained on 45 of the 50 infants. During each pneumogram recording, a log was kept by the mother to indicate sleep intervals, and all pneumogram recordings had a minimum of 8 hours of sleep time available for analysis. Pneumograms were hand scored and interpreted according to previously published methods.[6] Scoring was performed by individuals who were unaware that this study was being performed. Each 24-hour recording was analyzed for three primary measurements: brief apnea (≥6 seconds), periodic breathing, and longest apnea. Brief apneas were quantitated as the apnea density (A_6/D%), or total duration of all respiratory pauses of 6 seconds or more, expressed as a percent of total sleep time. Periodic breathing was defined in a standard manner and expressed as the number of episodes per 100 minutes of total sleep time. A pneumogram was interpreted as abnormal if the A_6/D%, the episodes of periodic breathing per 100 minutes, or the longest apnea exceeded the 95th percentile for the values present, using identical methods, in healthy full-term infants at 1 month of age: 0.92%, 2.9 episodes per 100 minutes, or 15 seconds, respectively.[6]

RESULTS

Pneumograms were performed at 2 weeks of age in 27 of 32 cocaine-exposed infants and in all 18 methadone-exposed infants. Five other cocaine-exposed infants who were also enrolled in the prenatal program had been unavailable for follow-up and failed to undergo pneumogram evaluation until after they presented after an apparent life-threatening episode requiring home resuscitation by paramedics. Following a thorough but unrevealing inpatient evaluation to identify other causes for these episodes, a diagnosis of apnea of infancy was established and a pneumogram was performed. Except for the lack of an earlier pneumogram, while the infants were still asymptomatic, and the subsequent development of apnea of infancy, these five mother/infant pairs were comparable with the other prenatal enrollees.

The pneumogram was abnormal[6] in all 5 cocaine-exposed infants presenting

Table 2.—Respiratory Pattern in Cocaine-Exposed Infants

	Clinical Status Before Pneumogram	
	Asymptomatic (N=27)	Symptomatic (N=5)
Age	7-14 d	4 wk
Apnea density*		
Mean ± SEM	0.6 ± 0.2	1.7 ± 0.3†
Median	0.1	1.4
Periodic breathing‡		
Mean ± SEM	0.9 ± 0.3	4.1 ± 0.9†
Median	0.2	3.5
Longest apnea, s		
Mean ± SEM	8.0 ± 2.15	10.6 ± 1.34
Median	8.0	10.0

*Apnea density is the total duration of all respiratory pauses of 6 seconds or more, expressed as percent of total sleep time.
†$P<.01$ (Mann-Whitney test).
‡Periodic breathing is expressed as number of episodes per 100 minutes of total sleep time.

Table 3.—Comparison of Pneumogram Values in Drug-Exposed Infants With Abnormal and Normal Respiratory Patterns*

	Drug-Exposed Infants		
		Abnormal Pneumogram (N=13)	
	Normal Pneumogram (N=37)	Before Theophylline	With Theophylline†
Apnea density‡	0.34 ± 0.3	2.1 ± 1.1	0.2 ± 0.1†
Periodic breathing§	0.36 ± 0.49	3.6 ± 1.8	0.2 ± 0.2†
Longest apnea, s	8.1 ± 1.8	10.5 ± 1.6	8.9 ± 2.5†

*Values are expressed as mean ± SEM.
†Theophylline treatment resulted in significant improvement in all 13 infants; $P<.02$ compared with the pretheophylline value (Mann-Whitney test).
‡Apnea density is the total duration of all respiratory pauses of 6 seconds or more, expressed as percent of total sleep time.
§Periodic breathing is expressed as number of episodes per 100 minutes of total sleep time.

with apnea of infancy, in 7 of the remaining 27 asymptomatic cocaine-exposed infants (25.9%), and in 1 of the 18 methadone-exposed infants. This frequency of abnormal pneumograms in the cocaine-exposed group (12 [38%] of 32) was significantly greater than in the methadone-exposed group (1 [6%] of 18) by χ^2 analysis ($\chi^2=4.56$; $P<.05$). The frequency of abnormal pneumograms was still significantly greater in the asymptomatic cocaine-exposed infants than in the methadone-exposed infants (7 of 27 vs 1 of 18, respectively; $P<.05$).

The frequency distribution for A_6/D%, periodic breathing, and longest apnea (Figure) for the cocaine- and methadone-exposed groups showed overlap with previously reported values in normal infants.[6] Analysis of group differences between the three groups of infants showed no statistically significant differences for periodic breathing or longest apnea, but A_6/D% was significantly greater in the cocaine-exposed group than in normal infants ($P<.05$, unpaired t test). In this study, each infant in whom longest apnea did exceed 15 seconds also had an abnormal value for A_6/D% and/or for periodic breathing.

The five infants not evaluated before the occurrence of symptomatic apnea (Figure, Table 2) had A_6/D% and periodic breathing values that were significantly higher than those in the asymptomatic cocaine-exposed infants.

Cocaine-exposed infants with abnormal pneumograms were evenly distributed between those infants whose mothers used cocaine throughout pregnancy and those whose mothers abstained from cocaine use after the first trimester. Two (17%) of the 12 cocaine-exposed infants with an abnormal pneumogram were also exposed prenatally to methadone.

The 37 cocaine- and methadone-exposed infants with a normal pneumogram did not receive any intervention intended to reduce the risk of a subsequent life-threatening event. The 13 infants with an abnormal pneumogram, however, began receiving theophylline therapy, beginning at 1.5 mg/kg per dose, administered every 6 hours.[8,9] In all 13 infants, a second pneumogram performed within 2 weeks of the first pneumogram was normal, at a peak theophylline level of 44 to 55 μmol/L; the values for A_6/D%, periodic breathing, and longest apnea (Table 3) were significantly less than the pretheophylline values and were now comparable with the normal pneumogram group values.

All 50 infants were subsequently followed up for a minimum of 6 months. In no instance was a home monitor used. No infant died of SIDS, and no apnea of infancy later occurred in the asymptomatic nonintervention group of 37 infants with normal pneumograms. The 13 infants with abnormal pneumograms that subsequently normalized during theophylline therapy were maintained on a regimen of theophylline until they were at least 6 months of age, longer if the pneumograms had not yet normalized. No apnea of infancy developed in the 8 asymptomatic infants, and no further apnea-related symptoms occurred in the 5 symptomatic infants.

COMMENT

Previous investigations of pregnancies complicated by maternal cocaine use have revealed an increased incidence of spontaneous abortions, abruptio placentae, and premature delivery, as well as impairment of neonatal interactive and state organization abilities.[10,11] The historical (retrospective) experience indicates that infants with intrauterine exposure to cocaine also appear to be at increased risk for SIDS.

The documentation of cocaine exposure as a risk factor for SIDS is consis-

tent with the risks that have been established for intrauterine exposure to other substances of abuse, such as narcotics.[1,2] In addition, the effects of secondary substances of maternal abuse (eg, cigarettes, alcohol, and marijuana) must be considered when evaluating cocaine-exposed infants' risk for SIDS. The narcotic-addicted women in our program had rates of cigarette, alcohol, and marijuana use similar to those of the cocaine-using women, but the retrospective group of cocaine-exposed infants had a greater incidence of SIDS than did the methadone-exposed infants, and the prospective group of cocaine-exposed infants had a greater incidence of respiratory pattern abnormalities, thus implying that cocaine exposure accounts for these increased rates. The interactive effects of secondary drugs with cocaine cannot be determined from the present study, but this type of analysis will be attempted when data from studies involving larger numbers of infants are available.

The pathophysiologic relationship between prenatal cocaine exposure and SIDS is unknown. In previous studies conducted in our Perinatal Center, it has been shown that infants with intrauterine exposure to drugs of abuse[12] had "down-regulation" of placental neurotransmitter receptors. Abnormalities or depletion of these receptor sites, especially if the same process occurs in the fetal brain, could be associated with impaired function of the normal neonatal respiratory control system and thus could, for example, result in prolonged and/or more frequent periods of apnea.

In a recent study, investigators speculated that elevated circulating catecholamine levels are associated with abnormal hypoxic arousal responses in children with apnea of infancy.[13] This would be consistent with the pharmacologic action of cocaine, in that cocaine acts at the peripheral nerve endings to block reuptake of norepinephrine, producing increased circulating levels of catecholamines.[14] Furthermore, norepinephrine is the neurotransmitter specifically affected by cocaine and is also the primary neurotransmitter in the locus coeruleus, the putative center of arousal[15]; deficient arousal responsiveness is an important component of the respiratory control system and may be essential for the occurrence of SIDS.[16] It is thus possible that cocaine may increase risk for cardiorespiratory pattern abnormalities and for SIDS by preventing normal intrauterine development of critical brain-stem structure and function as a consequence of disequilibrium of norepinephrine hemostasis, thus somehow altering normal maturation of cardiorespiratory control.

Sudden infant death syndrome occurs with increased frequency in preterm infants and in black infants,[3] but most of our infants were full term, and many were white. There has been a recent reemphasis of the role of both accidental and nonaccidental trauma as potential explanations of sudden death in infants.[17] Although home visits were not made in any of the SIDS families in our initial retrospective review, all infants dying of SIDS had autopsies performed, and no evidence of trauma was found.

The abnormal pneumograms in all five cocaine-exposed infants presenting with apnea of infancy should not lead one to conclude or to expect that all such infants would have an abnormal pneumogram. Normal respiratory pattern has generally been observed in at least 30% to 40% of patients with apnea of infancy, and there may be additional cocaine-exposed infants enrolled in the prenatal program who were unavailable for follow-up and subsequently developed apnea of infancy, but were evaluated elsewhere and found to have a normal pneumogram. Unfortunately, our experience with these five patients provides no new insights into the relationship between apnea of infancy, respiratory pattern, and risk for SIDS; the number of patients is too small, and subsequent intervention may have affected outcome. Finally, although no infants with normal respiratory pattern in our series died of SIDS, infants dying of SIDS can certainly have a normal neonatal pneumogram,[18] and at least one previously described drug-exposed infant who died of SIDS had a normal pneumogram.[19]

Our results provide no new insights into the potential usefulness of cardiorespiratory pattern in prospectively assessing SIDS risk, because there is no nonintervention control group. Similarly, our results provide no new insights into the potential usefulness of theophylline, because of the absence of a randomized placebo group. Even if a comprehensive intervention program might be effective in reducing SIDS incidence, a fact not yet in evidence, no conclusions can be reached as to what component(s) of the complex medical/psychosocial/educational support program might be most contributory.

We compared our respiratory pattern values in these 50 infants with previously reported values in normal infants at 1 month of age.[6] Although our drug-exposed infants were, on average, 2 weeks younger, respiratory pattern values do not differ at 2 vs 4 weeks of age.[20] For a similar reason, the differences in respiratory pattern values between the asymptomatic and symptomatic cocaine-exposed infants cannot be explained by the older age in the latter five infants; if there is any tendency at all between 2 and 4 weeks, it would be in the direction of lower values with increasing age, thus making the higher values observed even more significant.

Our prospective study was designed to determine whether cardiorespiratory pattern abnormalities occur at an increased frequency in a group of infants at increased epidemiologic risk for SIDS. In contrast to the retrospective survey of 66 exposed infants in whom no specific intervention was attempted (10 deaths), no infants died of SIDS in this prospective study. This difference in SIDS incidence (10 of 66 vs 0 of 50) is statistically significant ($\chi^2 = 3.9$; $P < .05$), but larger prospective studies are necessary to further assess the SIDS risk in cocaine-exposed infants and to assess whether any observed decrease in SIDS incidence is related to the medical treatment (ie, home monitoring and/or theophylline therapy), to the comprehensive psychosocial support/intervention program, or to some combination thereof.

In summary, prenatal cocaine exposure appears to be associated with an increased frequency of cardiorespiratory pattern abnormalities, even compared with heroin/methadone exposure. In our comprehensive neonatal follow-up program, which includes assessment of cardiorespiratory pattern and treatment of any observed abnormalities, we have thus far not observed any SIDS. Larger prospective studies will be necessary, however, to deter-

mine the pathophysiologic relationship between SIDS and prenatal drug exposure, and the extent to which the various components of a comprehensive prospective support/intervention program may contribute to a reduced SIDS incidence.

This study was supported in part by a grant (DA04103-01) from the National Institute on Drug Abuse, National Institutes of Health, Bethesda, Md, the Children's Research Guild, Chicago, Ill, and the Lillian S. Wells Foundation, Chicago, Ill.

Our thanks to Linda Klemke, for her assistance in data analysis, and to Mary Kesling, for her assistance in preparation of this manuscript.

References

1. Chavez CJ, Ostrea, Jr EM, Stryker JC, Smialek Z. Sudden infant death syndrome among infants of drug-dependent mothers. *J Pediatr.* 1979; 95:407-409.

2. Rosen TS, Johnson HL. Drug-addicted mothers, their infants, and SIDS. *Ann NY Acad Sci.* 1988;533:89-95.

3. Black L, David RJ, Brouillette RT, Hunt CE. Effects of birth weight and ethnicity on incidence of sudden infant death syndrome. *J Pediatr.* 1986; 108:209-214.

4. Chasnoff IJ, Burns WJ, Hatcher R. Polydrug- and methadone-addicted newborns: a continuum of impairment? *Pediatrics.* 1982;720:210-213.

5. Rosner MA, Keith L, Chasnoff IJ. The Northwestern University Drug Dependence Program: the impact of intensive prenatal care on labor and delivery outcomes. *Am J Obstet Gynecol.* 1982; 144:23-27.

6. Hunt CE, Brouillette RT, Hanson D, David RJ, Stein IM, Weissbluth M. Home pneumograms in normal infants. *J Pediatr.* 1985;106:551-555.

7. Hunt CE, Brouillette RT, Liu K, Klemka L. Day-to-day pneumogram variability. *Pediatr Res.* 1985;19:174-177.

8. Hunt CE, Brouillette RT, Hanson D. Theophylline improves pneumogram abnormalities in infants at risk for sudden infant death syndrome. *J Pediatr.* 1983;103:969-974.

9. Hunt CE, Brouillette RT. Methylxanthine treatment in infants at risk for sudden infant death. *Ann NY Acad Sci.* 1988;533:119-126.

10. Chasnoff IJ, Burns WJ, Schnoll SH, Burns KA. Cocaine use in pregnancy. *N Engl J Med.* 1985;313:666-669.

11. MacGregor SN, Keith LG, Chasnoff IJ, et al. Cocaine use during pregnancy: adverse perinatal outcome. *Am J Obstet Gynecol.* 1987;157:686-690.

12. Perry BD, Pesavento DJ, Kussie PH, U'Prichard DC, Schnoll SH. Prenatal exposure to drugs of abuse in humans: effects on placental neurotransmitter receptors. *Neurobehav Toxicol Teratol.* 1984;6:295-301.

13. Rodriguez AM, Warburton D, Keens TG. Elevated catecholamine level and abnormal hypoxic arousal in apnea of infancy. *Pediatrics.* 1987;79:269-274.

14. Ritchie JM, Greene NM. Local anesthesia. In: Gilman AG, Goodman LS, Gilman A, eds. *The Pharmacological Basis of Therapeutics.* 6th ed. New York, NY: Macmillan Publishing Co Inc; 1980:300-320.

15. Svensson TH. Brain norepinephrine neurons in the locus coeruleus and the control of arousal and respiration: implication for SIDS. In: von Euler C, Lagercrantz H, eds. *Neurobiology of the Control of Breathing.* New York, NY: Raven Press; 1986:297-301.

16. Hunt CE, Brouillette RT. Apnea and sudden infant death syndrome: 1987 perspective. *J Pediatr.* 1987;110:669-678.

17. Bass M, Kravath RE, Glass L. Death-scene investigation in sudden infant death. *N Engl J Med.* 1986;315:100-105.

18. Southall DP, Richards JM, de Swiet M, et al. Identification of infants destined to die unexpectedly during infancy: evaluation of predictive importance of prolonged apnea and disorders of cardiac rhythm or conduction. *Br Med J.* 1983;286:1092-1096.

19. Ward SLD, Schuetz S, Krishna V, et al. Abnormal sleeping ventilatory pattern in infants of substance-abusing mothers. *ADJC.* 1986;140:1015-1020.

20. Kelly DH, Stellwagen LM, Kaitz E, Shannon DC. Apnea and periodic breathing in normal full-term infants during the first twelve months. *Pediatr Pulmonol.* 1985;1:215-219.

CORRECTION

Incorrect Term.—The article titled "Advances in Pediatric Cardiology," published in the January issue of *AJDC* (*AJDC.* 1989;143:24), contained an incorrect term. In line 22 of column 2, the term "balloon" rather than "blade" should have been used.

Sucking and Breathing Patterns During Breast- and Bottle-feeding in Term Neonates

Effects of Nutrient Delivery and Composition

Oommen P. Mathew, MD, Jatinder Bhatia, MD

• We attempted to determine whether differences in milk composition or flow rate are the primary determinants in altering breathing pattern during nipple-feeding. In the first phase of the study, 15 neonates were studied during breast-feeding and bottle-feeding; in the second phase, 15 were evaluated during bottle-feeding of expressed human milk and formula. A reduction in inspiratory duration was observed with all feeding regimens. Moreover, significant prolongation in expiratory duration and reduction in breathing frequency were observed during bottle-feeding of formula and expressed human milk (compared with control); these effects were greater with formula feeding. Higher sucking frequency was observed during breast-feeding compared with bottle-feeding; no difference in sucking frequency or sucking pressure was observed between bottle-feeding of expressed human milk and formula. We conclude that most of the differences in sucking and breathing patterns between breast- and bottle-feeding can be attributed to nutrient delivery rather than nutrient composition.

(*AJDC*. 1989;143:588-592)

The goal of formula feeding in neonates has been to mimic human milk in composition and to deliver it through artificial nipples that will allow sucking patterns similar to those observed at the human breast. This is substantiated by the fact that the composition of artificial formulas, both for preterm and term neonates, have been "humanized" to more closely reflect human milk; furthermore, design features of various nipples have been altered to more closely resemble the human nipple. Be that as it may, there is a paucity of data regarding sucking and breathing patterns during breast-feeding, whereas sucking and breathing patterns during bottle-feeding have been studied more extensively.[1-7] Alteration of the breathing pattern during bottle-feeding primarily consists of a prolongation of expiratory duration (T_E) and a shortening of inspiratory duration (T_I).[3,4] A number of hypotheses, including laryngeal chemoreceptor stimulation and repeated swallowing, have been proposed to explain these findings.[1-4,8,9]

Stimulation of laryngeal chemoreceptors has been shown to alter the breathing pattern in animals and has been similarly implicated in human neonates.[1,10,11] In addition, an alteration in breathing pattern during swallowing is also well documented.[12-14] During the first few days of breast-feeding, milk flow is known to be markedly reduced. A reduction in milk flow would reduce the number of swallows. The difference in milk flow between bottle-feeding and breast-feeding in the first week, as well as the difference in composition between human milk and commercially available formulas, provided us an excellent opportunity to determine whether nutrient composition or milk delivery is the important determinant of the alteration in breathing pattern. We compared the sucking and breathing patterns of term neonates during breast-feeding and bottle-feeding of expressed human milk and formula.

SUBJECTS AND METHODS

Subjects

Term neonates whose mothers elected to breast-feed were eligible for enrollment in the study. The protocol was approved by the institutional review board, and parental consent was sought if the neonate met the following eligibility requirements: (1) free of major congenital anomalies or cardiopulmonary disease; (2) breast-fed; (3) gestational age between 38 and 42 weeks; and (4) Apgar scores greater than or equal to 5 and greater than or equal to 7 at 1 and 5 minutes, respectively. Mean (± SD) birth weight of the study neonates was 3351 ± 530 g, and they were studied at a mean postnatal age of 2.9 ± 1.4 days.

Methods

The study was conducted in two phases, with 15 neonates being studied in each phase. In the first phase, neonates were evaluated during breast- and bottle-feeding, and in the second phase, during bottle-feeding of expressed human milk and formula. In both phases, the neonates were studied during two consecutive feedings, but the feeding order was randomly assigned.

Mothers were asked to express their milk using a manual breast pump. Complete emptying was encouraged and this milk was then fed to their neonate from a bottle. During the bottle-feeding experiments, a standard commercially available 281.4-kJ/dL formula for term neonates was fed. The following variables were monitored: heart rate by standard electrocardiogram leads, respiratory efforts by respitrace bands (Ambulatory Monitoring Inc, New York, NY) placed around the chest and abdomen, and sucking pressure with a 5F catheter (Millar Instruments Inc, Houston, Tex). In the bottle-feeding studies (human milk or formula), the transducer catheter was passed through a standard commercially available nipple (Enfamil single-hole, Mead Johnson Nutrition Division, Evansville, Ind) so that its pressure-sensing tip

Accepted for publication December 20, 1988.

From the Division of Perinatal Pediatrics, Department of Pediatrics, University of Texas Medical Branch, Galveston.

Presented in part at the annual meeting of the American Pediatric Society/Society for Pediatric Research, Anaheim, Calif, April 30, 1987.

Reprint requests to Perinatal Pediatrics, University of Texas Medical Branch, Galveston, TX 77550 (Dr Mathew).

was just outside but close to the nipple hole; in breast-feeding studies, this catheter was taped to the breast so that its tip was close to the nipple and was inside the oral cavity during actual breast-feeding. This arrangement did not cause any problems with breast-feeding. Oxygen saturation was monitored with a pulse oximeter (Nellcor Inc, Hayward, Calif) in the first phase of the study. In the second phase of the study (comparison of bottle-feeding of formula with that of expressed human milk), a pneumotachograph attached to the nose was used to measure airflow as previously reported.[3] All of the variables monitored were recorded continuously on a Gould-Brush recorder (Gould Inc, Cleveland, Ohio).

Data Analysis

Twenty-three (77%) of 30 neonates exhibited an initial period of continuous sucking lasting at least 30 seconds, followed by intermittent sucking bursts during both feedings as previously reported.[3] Therefore, sucking and breathing patterns were analyzed separately for these two periods. The remaining neonates did not show a clear intermittent sucking pattern. Sucking patterns were not analyzed in 6 of 60 studies, because they were judged to be technically inadequate. Five of these studies were during breast-feeding. From the polygraphic records the following variables were evaluated:

1. Sucking frequency and sucking pressure were measured during the continuous and intermittent sucking periods.
2. Inspiratory and expiratory duration and breathing frequency (f) were determined.
3. The lowest heart rate during feeding was determined from electrocardiogram tracing. Bradycardia was defined as a heart rate of less than 100 beats per minute for at least three consecutive beats.
4. Although oxygen saturations were monitored during breast-feeding and bottle-feeding in all 15 neonates, technically satisfactory recordings were obtained only in 10 neonates. The lowest oxygen saturations during feeding were determined in these neonates.

Mean sucking frequency and sucking pressure during the initial continuous sucking phase and the subsequent intermittent sucking phase were determined for each neonate during breast-feeding and bottle-feeding.

Inspiratory duration, T_E, and f were determined during the control period (period prior to beginning of feedings), the continuous and intermittent sucking periods, and the intervening pauses. Mean values were calculated for each period during both breast- and formula-feeding.

Sucking pattern and breathing pattern during the second phase of the study (expressed human milk vs formula) were analyzed like the initial phase, except that the values of the respiratory variables were calculated in the first phase from the respiratory movement of the abdomen, whereas nasal airflow was used in this phase. To minimize interventions during breast-feeding, a nasal flowmeter was not used in the first phase of the study with breast- or bottle-feeding. The validity of measurements from abdominal movement was tested by comparing the values with those obtained from nasal airflow in pilot studies. Moreover, the values obtained during bottle-feeding of formula were similar in the two phases of the present study (see below). Data were analyzed using ANOVA and *t* tests, where appropriate. $P<.05$ was considered significant.

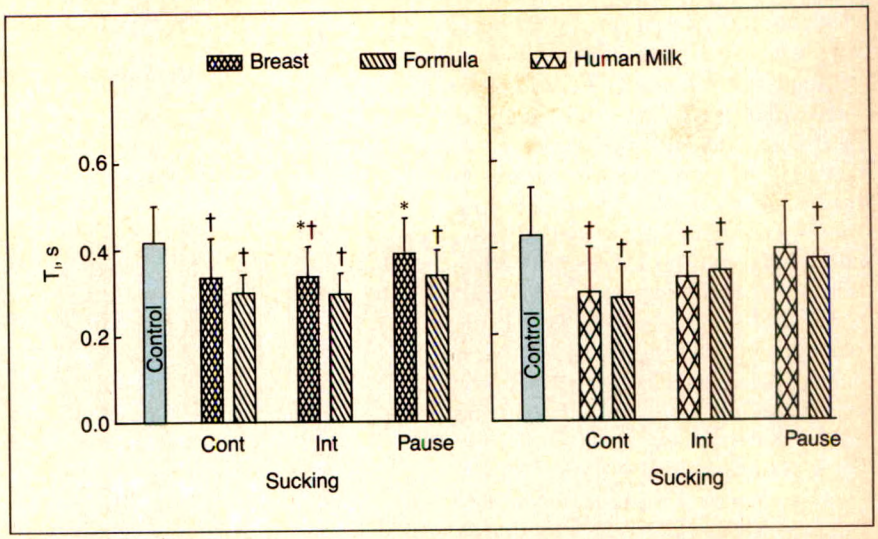


Fig 1.—Changes in inspiratory duration (T_I) during feeding. Values of inspiratory duration during control period, continuous (Cont) and intermittent (Int) sucking phases, and intervening pauses for the first phase (left, breast vs formula) and the second phase (right, expressed human milk vs formula) are shown. Dagger indicates $P<.05$ compared with control; asterisk, $P<.05$ compared with formula.

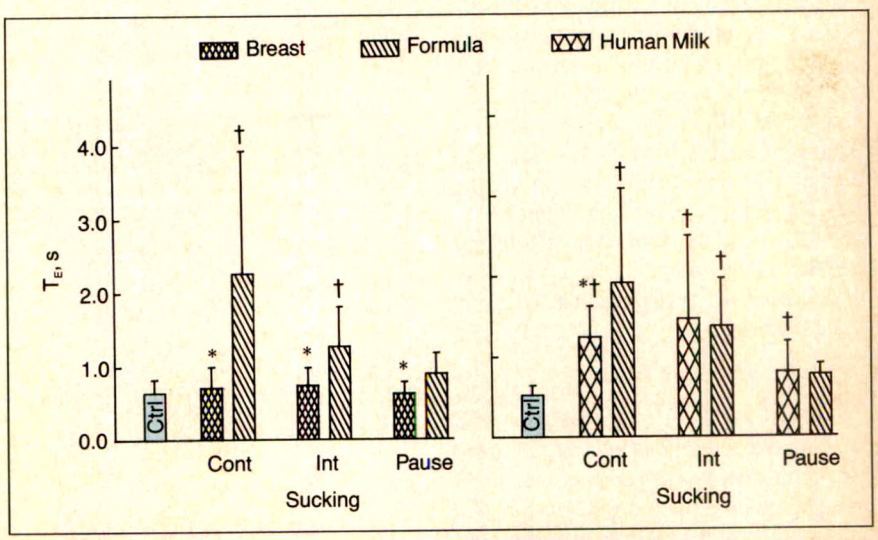


Fig 2.—Changes in expiratory duration (T_E) during feeding. Values of expiratory duration during control (Ctrl) period, continuous (Cont) and intermittent (Int) sucking phases, and intervening pauses for the first phase (left, breast vs formula) and the second phase (right, expressed human milk vs formula) are shown. Note that expiratory duration is unchanged during breast-feeding but is markedly prolonged during formula feeding and expressed human milk feeding. Dagger indicates $P<.05$ compared with control; asterisk, $P<.05$ compared with formula.

RESULTS

Breathing Pattern

Breast- vs Bottle-feeding.—Compared with control values, a significant

reduction in T_I, a prolongation in T_E, and a reduction in f were observed during continuous and intermittent sucking periods of bottle-feeding (Figs 1 through 3).[1-3] Even though a significant reduction in T_I was observed during breast-feeding when compared with control values, no significant changes occurred either in T_E or f (Figs 1 through 3). When the two feeding regimens were compared, the prolongation in T_E and the reduction in f were significantly greater during bottle-feeding compared with breast-feeding ($P<.05$). Bradycardia was observed in two neonates during bottle-feeding and none during breast-feeding. Oxygen saturation below 90% was observed in 5 of 10 neonates during bottle-feeding and in only 2 of 10 neonates during breast-feeding.

Expressed Human Milk vs Formula.—A significant reduction in T_I, a prolongation in T_E, and a reduction in f were observed during the two sucking phases of both human milk and formula feeding (Figs 1 through 3). When the two feeding regimens were compared, the only significant differences were the greater prolongation in T_E and the reduction in f during the continuous sucking period ($P<.05$) of formula feeding. None of the neonates developed bradycardia during breast milk feeding, whereas one neonate developed bradycardia during formula feeding.

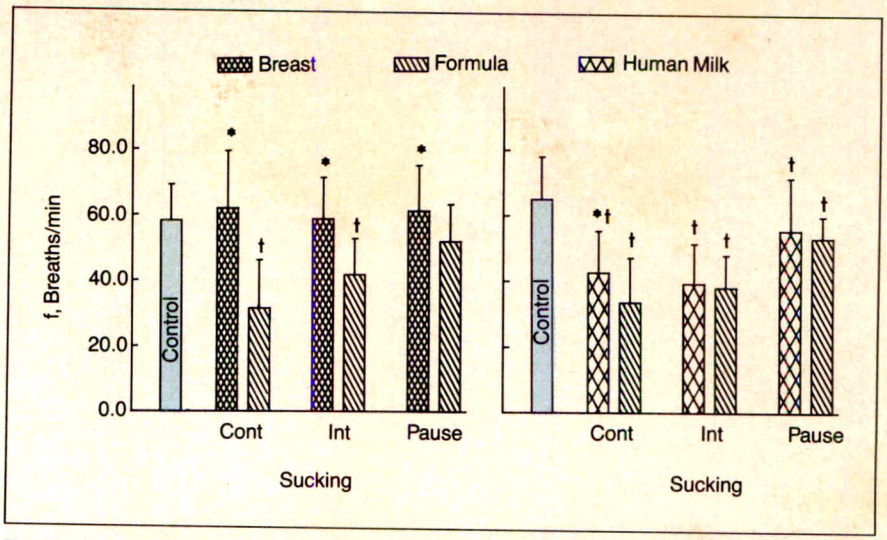


Fig 3.—Changes in breathing frequency (f) during the various feeding regimens. Values of breathing frequency during control period, continuous (Cont) and intermittent (Int) sucking phases, and intervening pauses for the first phase (left, breast vs formula) and the second phase (right, expressed human milk vs formula) are shown. Changes in breathing frequency are observed with formula feeding and expressed human milk feeding only. Dagger indicates $P<.05$ compared with control; asterisk, $P<.05$ compared with formula.

Sucking Pattern

Breast- vs Bottle-feeding. — The sucking frequency was 88.3 ± 21.2 sucks per minute during the initial continuous sucking phase and 80.4 ± 16.5 sucks per minute during the intermittent sucking phase of breast-feeding. On the other hand, the mean sucking frequency during bottle-feeding was 62.6 ± 7.3 sucks per minute during the continuous sucking phase and 58.3 ± 9.9 sucks per minute during the intermittent sucking phase (Table). These values differed significantly ($P<.05$) from corresponding values during breast-feeding.

During breast-feeding, the mean sucking pressure was 151.9 ± 44.2 cm H_2O in the continuous and 155.5 ± 72.6 cm H_2O in the intermittent sucking phases. Corresponding values during bottle-feeding were 213.6 ± 74.4 and 169.5 ± 70.0 cm H_2O, respectively. These values were not significantly different from those observed during breast-feeding.

Sucking Pattern During the Various Feeding Regimens*

Feeding	Continuous Sucking		Intermittent Sucking	
	Frequency, Sucks/min	Pressure, cm H_2O	Frequency, Sucks/min	Pressure, cm H_2O
Breast	88.3 ± 21.2	151.9 ± 44.2	80.4 ± 16.5	155.5 ± 72.6
Bottle	62.6 ± 7.3†	213.6 ± 74.4	58.3 ± 9.9†	169.5 ± 70.0
Human milk	72.4 ± 13.3	214.1 ± 58.0	67.9 ± 10.6	164.5 ± 53.9
Formula	67.7 ± 7.8	196.0 ± 72.3	67.2 ± 14.9	138.0 ± 52.2

*Values are the mean ± SD.
†$P<.05$ vs breast-feeding.

Expressed Human Milk vs Formula.—The mean sucking frequency during human milk feeding was 72.4 ± 13.3 sucks per minute in the continuous sucking phase and 67.9 ± 10.6 sucks per minute in the intermittent sucking phase. Similar values for the respective phases during formula feeding were 67.7 ± 7.8 and 67.2 ± 14.9 sucks per minute. The peak pressures observed during the two phases of human milk feeding were 214.1 ± 58 cm H_2O and 164.5 ± 53.9 cm H_2O, whereas values of 196.0 ± 72.3 cm H_2O and 138 ± 52.2 cm H_2O were observed during the two corresponding phases of formula feeding. None of these differences were statistically significant.

COMMENT

Significant alterations in breathing pattern during bottle-feeding have been demonstrated in term neonates.[3] Healthy neonates between 1 and 5 days of age demonstrated a significant reduction in minute ventilation accompanied by a decrease in f during the continuous sucking phase of a feeding. In the intermittent sucking phase, smaller yet significant changes compared with control values were observed. Durand and coworkers[2] studied term neonates in the

neonatal period who were either breast- or bottle-fed. Although the primary focus of their study was to determine the ventilatory response to breathing carbon dioxide, certain differences in breathing patterns between breast- and bottle-fed neonates could be discerned. In the absence of CO_2, bottle-feeding resulted in a greater reduction in inspiratory time than breast-feeding; however, no differences in minute ventilation, tidal volume, and respiratory frequency were observed between breast- and bottle-fed neonates. Moreover, the reduction in the slope of the ventilatory response to CO_2 was greater in the bottle-fed neonates, but this trend did not achieve statistical significance. These studies suggested differences in breathing pattern between breast- and bottle-fed neonates, but the number of neonates studied in each group was small.

Our results indicated that substantial alterations in breathing pattern occurred during breast- and bottle-feeding. However, in the first phase of the study it was not clear whether the greater alteration with formula feeding was due to differences in milk composition or milk delivery. Clearly the milk flow is lower during breast-feeding, since these neonates were studied by design well before lactation was established. Therefore, the difference in breathing pattern between the two human milk feedings (breast-feeding vs bottle-feeding of expressed human milk) can only be attributed to the difference in milk delivery. However, this difference may disappear when lactation is well established. Similar differences in breathing pattern between the two bottle-feedings (expressed human milk vs formula) are primarily due to differences in composition of milk. Since greater differences in breathing pattern were observed between breast- and bottle-feedings than the two types of bottle-feedings, we can conclude that nutrient delivery plays a greater role in altering the breathing pattern.

Repeated swallowing appears to be the primary mechanism for reducing ventilation during oral feeding. Interruptions of airflow of approximately 1.0 second occur with each swallow.[13] Repeated swallowing, therefore, decreases the time available for breathing and, consequently, decreases minute ventilation. Decreases in transcutaneous oxygen tension and oxygen saturations during bottle-feeding are being recognized with increasing frequency, especially in preterm neonates and in neonates with bronchopulmonary dysplasia.[4,15,16] Decreases in oxygen saturation during oral feeding were observed even in term neonates. A greater number of bottle-fed neonates exhibited oxygen saturation below 90% compared with breast-fed neonates (5 of 10 vs 2 of 10). Decreasing the milk flow per suck may minimize the feeding-related oxygen desaturations in these neonates by increasing the time available for breathing through a reduction in the number of swallows per unit time. Premature neonates and/or neonates with bronchopulmonary dysplasia may benefit from such a change but only at the expense of increasing the feeding time.

The fact that there are only minimal differences between human milk and formula feeding is not entirely consistent with the preliminary report by Johnson and Salisbury.[1] These investigators observed marked differences between the two feeding regimens. Variances in the composition of the formula could account for the differences; however, both human milk and currently used formulas are relatively low in chloride ions. Hence, apnea should be expected to occur with both feeding regimens through the stimulation of laryngeal chemoreceptors. But, unlike the study by Johnson and Salisbury,[1] no great difference in the incidence of apnea was observed between human milk– and formula-fed neonates in the present study, as well as in another recent study.[17] Nevertheless, these studies do not necessarily exclude a role for laryngeal chemoreceptors. On the contrary, on the basis of low chloride ion concentration in human milk and formula, as well as the prolongation of T_E, one could argue that laryngeal chemoreceptors indeed play a role in the alteration of breathing pattern. These effects can be minimized by rapid removal of the stimulus from the laryngeal-epilaryngeal area by swallowing and/or regulating milk flow. It is quite possible that the milk flow may have been higher in the study by Johnson and Salisbury,[1] resulting in greater stimulation of laryngeal nerve endings.

Sucking frequency is reported to vary from 40 to 90 sucks per minute[7,14]; slower sucking rates are observed with nipples that allow more rapid flow of milk and vice versa.[14] The sucking frequency observed during the various feeding regimens in our study fell within this range. However, the sucking frequency with breast-feeding was significantly higher than that during bottle-feeding. The lack of difference in the sucking frequency between the two bottle-feeding regimens (expressed human milk and formula) indicated that the higher sucking frequency with breast-feeding was due to milk delivery rather than milk composition. Sucking pressure varies markedly among the various studies. Earlier studies, summarized by Halverson,[6] indicated that the pressure ranges from 3 to 14 mm Hg in some studies to 60 to 150 mm Hg in others; sucking pressures reported in recent studies vary between 50 and 200 mm Hg.[5] Most of the variation in pressures reported appear to be due to methodological differences. Shape and consistency of the nipple as well as the size of the nipple hole may all play a role in altering this response. Moreover, in a number of studies, milk was delivered through a feeding tube attached to the nipple; because of high flow, pressures generated were likely to be lower in these studies than those observed during actual bottle-feeding. The differences in sucking pressure and rate observed herein between breast-feeding and formula feeding are due to milk delivery (ie, flow rate and/or difference in nipple) rather than composition, since no differences were seen when the sucking patterns between expressed human milk and formula feedings were compared.

In summary, differences in sucking and breathing pattern were observed when breast- and bottle-feedings were compared. Most of these differences appeared to be due to differences in milk flow rather than composition.

This investigation was supported in part by grants from the National Institutes of Health (NIH), Bethesda, Md (HL-32921); Mead-Johnson Nutrition Division, Evansville, Ind; and March of Dimes Birth Defects Foundation (6-470).

Dr Mathew was the recipient of the clinical investigator award (HL-01156) from NIH.

We thank Mary Belan, Curtis P. Cowen, and Sally Sosa for their technical assistance.

References

1. Johnson P, Salisbury DM. Sucking and breathing pattern during artificial feeding in the human neonate. In: Bosma JF, Showacre J, eds. *Development of Upper Respiratory Anatomy and Function*. Rockville, Md: US Department of Health, Education and Welfare; 1975:206-209.
2. Durand M, Leahy FN, MacCallum M, Cates DR, Rigatto M, Chernik V. Effect of feeding on the clinical control of breathing in the newborn infant. *Pediatr Res*. 1981;15:1509-1512.
3. Mathew OP, Clark ML, Pronske ML, Luna-Solarzano HG, Peterson MD. Breathing pattern and ventilation during oral feeding in term newborn infants. *J Pediatr*. 1985;106:810-813.
4. Shivpuri CR, Martin RJ, Carlo WA, Fanaroff AA. Decreased ventilation in preterm infants during oral feeding. *J Pediatr*. 1983;103:285-289.
5. Sameroff AJ. Apparatus for recording sucking and controlling feeding in the first days of life. *Psychol Sci*. 1965;2:355-356.
6. Halverson HN. Infant sucking and tensional behavior. *J Genet Physiol*. 1938;53:365-430.
7. Kaye H. Infant sucking behavior and its modification. In: Lippsitt LP, Spiller CC, eds. *Advances in Child Development and Behavior*. Orlando, Fla: Academic Press Inc; 1967:1-52.
8. Perkott EN, Vaughn RL. Evidence for a laryngeal chemoreflex in some human infants. *Acta Paediatr Scand*. 1982; 71:969-972.
9. Davies AM, Koening JS, Thach BT. Upper airway chemoreflex responses to saline and water in preterm infants. *J Appl Physiol*. 1988;64:1412-1420.
10. Storey AT, Johnson P. Laryngeal water receptors initiating apnea in the lamb. *Exp Neurol*. 1975;47:42-55.
11. Boggs DF, Bartlet D Jr. Chemical specificity of a laryngeal apneic reflex in puppies. *J Appl Physiol*. 1982;53:455-462.
12. Nishino T, Yonezawa T, Honda Y. Effects of swallowing on the pattern of continuous respirations in human adults. *Am Rev Respir Dis*. 1985;132:1219-1222.
13. Wilson SL, Thach BT, Brouillette RT, Abuosba YK. Coordination of breathing and swallowing on human infants. *J Appl Physiol*. 1981;50:851-858.
14. Mathew OP. Regulation of breathing pattern during feeding: role of suck, swallow and nutrients. In: Mathew OP, Sant' Ambrogio G, eds. *Respiratory Function of the Upper Airway*. New York, NY: Marcel Dekker Inc; 1988:535-560.
15. Rosen CL, Glaze DG, Frost Jr JD. Hypoxemia associated with feeding in the preterm infant and full-term neonate. *Am J Dis Child*. 1984; 138:623-628.
16. Garg M, Kurzner SI, Bautista DB, Keens TG. Clinically unsuspected hypoxia during sleep and feeding in infants with bronchopulmonary dysplasia. *Pediatrics*. 1988;81:635-642.
17. Guilleminult C, Coons S. Apnea and bradycardia during feeding in infants weighing >2000 gm. *J Pediatr*. 1984;104:932-935.

CORRECTION

Incorrect Author's Name.—In the letter titled "Cutis Verticis Gyrata and Chromosomal Abnormalities," published in the March issue of *AJDC* (*AJDC*. 1989;143:269), an author's name was cited incorrectly in the signature. The first author's name is Romana Marini, MD.

For the symptoms of allergic rhinitis...

DESIGNED TO DELIVER

Now NASALCROM® is available in the ready-to-use pump spray your patients have been asking for! The new NASALMATIC® fully-assembled unit comes in two convenient sizes: For your chronic allergic rhinitis patients, the *new* 26 mL size is a handy, economical alternative to the purchase of frequent refills. For your patients with seasonal symptoms, the regular 13 mL size is ideal.

Inside the new NASALCROM unit is the proven formula patients rely on for relief of sneezing, itching, runny nose, and congestion.[1,2] NASALCROM provides protection from the first dose[1] and symptom relief within days.[2] And it works without the annoying side effects typical of other first-line allergic rhinitis medications.[3,4]

Nonsedating NASAL SOLUTION, 40 mg/mL

NASALCROM®

(cromolyn sodium/FISONS)

IN THE NEW FULLY-ASSEMBLED UNITS (26 mL AND 13 mL)

Please see adjacent page for Brief Summary of Full Prescribing Information.

NASAL SOLUTION, 40 mg/mL

NASALCROM®

(cromolyn sodium nasal solution, USP)

Brief Summary

DESCRIPTION: Each milliliter of NASALCROM® Nasal Solution (cromolyn sodium nasal solution, USP) contains 40 mg cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA (edetate disodium) to stabilize the solution.

INDICATIONS: NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.

CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.

PRECAUTIONS: General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy.

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphylaxis.

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

CAUTION: Federal law prohibits dispensing without prescription.

References:

1. Pelikan Z, Pelikan-Filipek M: The effects of disodium cromoglycate and beclomethasone dipropionate on the immediate response of the nasal mucosa to allergen challenge. *Ann Allergy* 1982;49:283-292.
2. Data on file, Fisons Corporation. From perennial allergic rhinitis trial by Wittig HJ, with Cohan RM, Bloom FL, Rhoades RB, et al.
3. *Physicians' Desk Reference® (PDR®),* ed 42. Oradell, NJ, Medical Economics Co Inc, 1988. Beconase® (beclomethasone dipropionate, USP), pp 1004-1005; Seldane® (terfenadine), pp 1426-1427.
4. *Physicians' Desk Reference for Nonprescription Drugs® (PDR®),* ed 9. Oradell, NJ, Medical Economics Co Inc, 1988. Afrin® (oxymetazoline hydrochloride), p 685; Chlor-Trimeton® (chlorpheniramine maleate), pp 686-687; Actifed® (pseudoephedrine hydrochloride, triprolidine hydrochloride), p 530; Sudafed® (pseudoephedrine hydrochloride), pp 533-534.

FISONS

Pharmaceuticals
Prescription Products
Rochester, NY 14623

© 1989 Fisons Corporation

FIS-048

Secondary Disorders of the Complement System

Lawrence F. Eichenfield, MD, Richard B. Johnston, Jr, MD

The complement system is a principle mediator of inflammation and serves as an important arm of the body's immune response. It was first discovered as a heat-sensitive serum factor necessary for bacterial lysis in the presence of specific antibody. How it "complements" the antigen-antibody interaction and mediates inflammation has been the subject of intensive research.

The complement system consists of 19 well-defined plasma proteins that interact with each other and with cell membranes. The function of many of these proteins has been defined through the study of natural deficiency states—the primary, inherited complement deficiencies. While much has been written about these,[1-4] there has been relatively little work addressing secondary disorders of complement. The purpose of this article is to survey diseases in which complement deficiency is secondary to some more primary disorder (Table 1). In most cases the complement deficiency contributes to the clinical presentation or pathogenesis of the underlying disease.

There are many excellent reviews of how the complement system functions,[2,5,6] and we will not attempt to reproduce them here. In brief, complement effects are mediated by two pathways: the classical and the alternative. The system consists of distinct component proteins, including regulators and inhibitors. Components are designated by numbers in the classical pathway and by letters in the alternative pathway. Component fragments are designated by lowercase letters (eg, C3a and C3b), and components that are active enzymes by a superscript bar (eg, $C\bar{1}$).The components assemble sequentially, the early ones (C1, C2, C3, and C4) forming active enzymes, which cleave other proteins, in a "cascading" fashion. The classical pathway is stimulated by antigen-antibody complexes and antibody-coated targets. The alternative pathway does not require the presence of antibody; it may be activated by particulate activators, including endotoxin and aggregated immunoglobulins. The pathways meet through a common set of late-acting components (Figure).

Effects of complement activation include release of vasoactive mediators and chemoattractants, opsonization, neutralization of endotoxin, solubilization of immune complexes, and formation of conduits in cell membranes, causing lysis (Table 2). Complement proteins can be consumed or altered in the process of the immune response, with profound effects on the evolution and expression of disease.

Most secondary complement deficiencies are due to complement consumption, decreased synthesis, or increased catabolism. In some clinical states it is clear how complement plays an important role in pathophysiology; in others the mechanism is less clear. In any case, unlike inherited complement deficiencies, secondary disorders can be found commonly, and their recognition may allow us insight into important functions of the complement system and into the pathogenesis of disease.

Accepted for publication December 19, 1988.

From the Department of Pediatrics, University of Pennsylvania School of Medicine, and The Children's Hospital of Philadelphia, Pa.

Reprint request to The Children's Hospital, Department of Pediatrics, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Johnston).

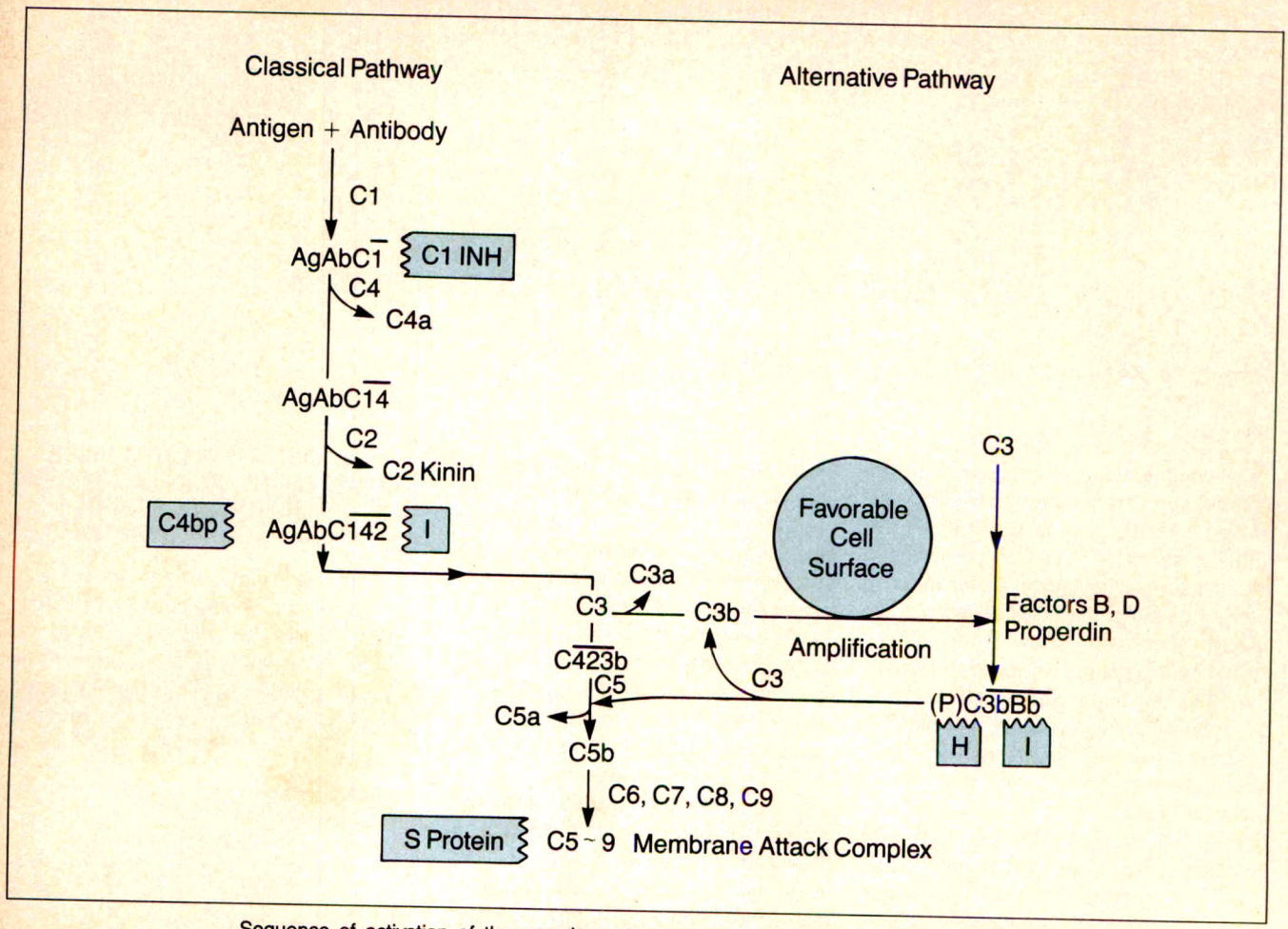
SECONDARY DISORDERS OF COMPLEMENT DUE TO ACTIVATION AND CONSUMPTION

Immune Complex Disease

Immune complexes can induce consumption of complement primarily through the classical pathway, as C1 binds to antibody in the complex and triggers the cascade. In many autoimmune diseases, circulating immune

Table 1.—Secondary Disorders of the Complement System

Disorders due primarily to activation and consumption
Immune complex diseases
Sickle cell disease
Postperfusion, dialysis, and leukapheresis syndromes
Infection
Thermal injury
Adult respiratory distress syndrome
Chronic hypocomplementemic nephritis
Acute pancreatitis
Atheroembolic disease
Reaction to radiographic contrast media
C1 inhibitor deficiency with B-cell lymphoproliferative disorder or autoantibody to the inhibitor
Hypocomplementemic vasculitis syndrome
Porphyria
Disorders due primarily to decreased synthesis
The newborn state
Malnutrition and anorexia nervosa
Liver cirrhosis
Reye's syndrome
Hepatic failure
Disorders due primarily to increased catabolism
Increased C1q catabolism associated with hypogammaglobulinemia
Nephrotic syndrome
Disorders due primarily to deficiency of noncomplement serum or membrane protein
Paroxysmal nocturnal hemoglobinuria
Decreased alternative pathway function associated with hypogammaglobulinemia, β-thalassemia major, or splenectomy



Sequence of activation of the complement components of the classical and alternative pathways. The classical pathway is initiated when the first component of complement (C1) binds to IgG or IgM antibodies (Ab) fixed to antigen (Ag). Activated C1, composed of three subcomponents C1q, C1r, C1s, reacts with C4 and C2 to generate C42, which is a C3-cleaving enzyme. C423b is formed, which in turn cleaves C5. A large fragment of C3 (C3b) is a powerful opsonin, and C5 activation leads to assembly of C56789 (C5~9), known as the membrane attack complex. The alternative pathway requires C3b, which may be generated as a byproduct of the classical pathway or from the alternative pathway through activity of a C3-cleaving enzyme formed from C3 and factor B (C3bBb). Alternative pathway cleavage of C3 can amplify classical pathway activity. Properdin (P) can bind C3bBb, stabilizing this important cleaving enzyme and protecting it from inactivation by factors H and I. The alternative pathway enzyme C3bBbC3b can cleave C5, paralleling activity of C423b of the classical pathway. Inhibitors (enclosed in notched boxes) act at several key sites: C1 inibitor (C1-INH) inhibits C1s, factor I inactivates C4b and C3b, factor H accelerates inactivation of C3b by I, and an analogous factor, C4 binding protein (C4bp), accelerates cleavage of C4b by I.

complexes play an important role, and there is increasing evidence that a complement-dependent system is important in immune complex elimination. Systemic lupus erythematosus (SLE) has been well studied in this respect. Complement depletion often parallels disease activity and is more pronounced in patients with active renal disease.[7] In these patients, serum levels of C1q, C4, C2, and C3 are decreased. Decreased levels of factor B have also been observed. C1q, C4, and C3 can be frequently detected in the kidney by immunofluorescence.[7] Deposition of insoluble immune complexes in tissues can activate complement by both the classical and alternative systems, leading to assembly of the membrane attack complex, C5~9.[8] This complex has been seen in biopsy specimens of affected skin at the dermoepidermal junction and in glomeruli of kidneys in SLE.[9,10] In active SLE the attack complex is induced, as well as a noncytolytic form in serum after binding of the inhibitor S protein, forming SC5-9. This complex can be measured in serum as an indicator of SLE activity, and the assay is more sensitive than quantitation of C3, C4, or total hemolytic complement (CH_{50}).[11]

Another indicator of the role of complement in SLE may be the relative deficiency of complement receptor 1 (CR1), the receptor for C3b, on red and white blood cells in active disease. There is

Table 2.—Activities of the Complement System

Complement Product	Biologic Activity
C14, C1423	Viral neutralization
C3a	Suppression of antibody response
C4a, C3a, C5a	Anaphylatoxin (vasoactive mediator release, increase of vascular permeability)
C3b	Opsonization; enhanced cell-mediated immunity; solubilization of immune complexes
C3 cleavage product	Granulocyte induction
C5a	Chemotaxis; granulocyte aggregation; enhanced antibody response
C1-5 (? others)	Endotoxin inactivation
C1-9	Cell lysis (viruses, virus-infected cells, tumor cells, *Mycoplasma*, protozoa, spirochetes, bacteria, host cells)

evidence that this receptor binds immune complexes and may prevent tissue damage by carrying complexes to the macrophage system. The reduced number of CR1s in many patients with SLE may be partially genetic in origin.[12] However, evidence has shown that receptors are depleted in active disease due to accelerated catabolism of CR1 in association with increased complement activation at the cell surface,[13] and in some cases due to autoantibodies to CR1.[14] With receptor depletion there may be a loss of "buffering" function, with increased deposition of complexes in susceptible tissue.[8]

Immune complex formation and hypocomplementemia have also been observed in a variety of other conditions, including subacute bacterial endocarditis, serum sickness, infectious mononucleosis, acute viral hepatitis, Felty's syndrome, primary biliary cirrhosis, and lepromatous leprosy.[15-21] There is strong evidence for immune complex–induced complement activation in rheumatoid arthritis.[22] Circulating immune complexes and decreased C3 have also been reported in dermatitis herpetiformis and celiac disease.[23]

Sickle Cell Disease

Children, and less often adults, with sickle cell disease are susceptible to pyogenic infections, especially due to pneumococci and *Haemophilus influenzae*. Associated abnormal phagocytic clearance with functional hyposplenia is a major factor in predisposing these individuals with hemoglobinopathy to infection.[24] However, there are other defects that may contribute to the problems. Serum from some patients with sickle cell disease has reduced ability to opsonize pneumococci via the alternative complement pathway despite normal ability through the classical pathway.[25,26]

There is also deficient bacteriolysis and opsonization of *Salmonella* through the alternative pathway.[27] Another subgroup of children with sickle cell disease has abnormal classical pathway opsonization abilities, with decreased deposition of C3 onto pneumococci.[28] In young children with homozygous sickle cell disease it has been shown that levels of C3 are significantly lower than levels in normal children.[29] There is evidence that the complement deficiency of sickle cell disease may be due to activation of complement in the circulation or tissues.[30] The alternative pathway may be activated in vitro by free hemoglobin or red blood cell stroma. One or both of these products of intravascular hemolysis may be active in sickle cell disease as reflected by a positive correlation between plasma hemoglobin and levels of the inactive product of C3 cleavage, C3d.[31,32]

Postperfusion, Dialysis, and Leukapheresis Syndromes

Cardiopulmonary bypass, renal dialysis, and leukapheresis are associated with a variety of adverse reactions. These include hemolysis, leukopenia, coagulopathy, and the postperfusion syndrome, characterized by increased capillary fragility, fever, shock, and multisystem dysfunction. It has become clear that complement activation by exchange membranes plays an important part in some of these reactions.[33-37] Cardiopulmonary bypass has been the most studied. Complement anaphylatoxins C3a and C5a are generated after bypass, and together with granulocyte activation may mediate many of the postperfusion syndrome symptoms.[33,36] The C5b~9 complement complexes are deposited on erythrocytes and granulocytes during bypass. Intravascular hemolysis is seen in all patients, and antibody to the membrane attack complex (MAC) (C5b~9) has been demonstrated on red blood cell ghosts.[36] This elegantly displays the power of the complete complement sequence. The terminal complement attack complex localizes on the red blood cell membrane. This C5b-9 "pore-former" complex is a cylinder with a lipophilic outer layer and hydrophilic inner layer, which allows extrusion of cell contents and lysis. Evidence of the MAC is seen on membranes of lysed red blood cells, but not on intact cells.

Infection

Infections can activate complement in a variety of ways. Immune complexes formed by antibody interacting with microbes can activate early complement components. Infections can also activate complement in the absence of demonstrable immune complexes, as seen in gram-negative bacteremia and shock. Bacteria, endotoxin, or both directly activate the alternative pathway and consume C3.[38,39] Gram-negative bacteremia without shock can activate the complement system, but without serious depletion of component levels.[38-40]

Activation of the alternative pathway and complement depletion has been associated with pneumococcal pneumonia,[41] cryptococcal septicemia,[42] and typhoid fever.[43] *Haemophilus influenzae* type b has been shown to have similar activity in vitro.[44] Some viruses have also been found to activate the alternative pathway in vitro,[45] and complement activation seems important in the pathogenesis of dengue hemorrhagic shock[46] and Argentine hemorrhagic fever.[47] Malarial paroxysms have been associated with substantial decreases in C1, C4, and C2.[48] Severe viral hepatitis B may be accompanied by complement depletion due to impaired synthesis as well as activation by immune complexes (explained

in the "Liver Cirrhosis, Reye's Syndrome and Hepatic Failure" section below), and may place the individuals at increased risk for meningococcemia.[49]

Acquired Immunodeficiency Syndrome

Studies of patients with acquired immunodeficiency syndrome have not revealed consistent deficiencies in complement components, with CH_{50}, C3, and C4 reported as normal.[50] However, there is evidence of C3 activation as measured by plasma C3 cleavage products (C3bi/C3d-g) and increased circulating immune complexes bearing complement fragments consistent with activation of the alternative pathway (C3bi, with absence of C1q). Erythrocyte receptors for C3b (CR1) are observed to be decreased, and this correlates with increased serum immune complexes. While the mechanism of the decreased expression of CR1 and circulating immune complexes is not known, it may be important in the pathogenesis and disease expression.[51]

Thermal Injury and Adult Respiratory Distress Syndrome

Burn injury can induce massive activation of the complement system within hours of injury.[52] Complements C3a and C5a are produced, stimulating neutrophils to aggregate and to sequester in the lungs.[53,54] These events probably play an important role in the development of adult respiratory distress syndrome after burn injury. The alternative pathway seems to be activated directly by injured tissue of burn wounds, and this is important early in the clinical course. Complement activation is prolonged for weeks, correlating with elevated levels of C4 fragments (C4a-des-Arg), arguing for classical pathway activation as well.[55] It appears that C5a induces neutrophil degranulation and depresses neutrophil chemotaxis by producing a receptor desensitization.[56] These effects and depressed opsonization due to complement deficiency undoubtedly contribute to the dangerous predisposition to infection in burn injury.[57]

Studies support complement activation and pulmonary granulocyte entrapment as having a pathogenic role in adult respiratory distress syndrome due to insults other than burns, including sepsis and severe trauma.[53,57-60] Complement activation as reflected by C3a, a C3a split product (C3a des Arg), C5a, and decreased CH_{50} has been correlated with development and severity of adult respiratory distress syndrome in patients at risk.[53,57]

Chronic Hypocomplementemic Nephritis

Depression of serum complement is a common feature of many types of acute nephritis. In some acute disorders, such as poststreptococcal nephritis, complement levels return to normal as the nephritis subsides. However, in some patients, particularly those with membranoproliferative glomerulonephritis, low complement levels (especially C3) persist.[61,62] In 1969 a factor was described in the serum of some of these patients that accelerates the cleavage of C3 in serum.[63] The factor was termed *C3 nephritic factor.* This factor has been shown to be an IgG autoantibody to the alternative pathway C3 convertase ($C\overline{3bBb}$), which acts by suppressing the decay promotor factor H. The stabilization of C3 convertase allows consumption of C3 and results in low serum levels.

A nephritic factor that binds to the classical pathway convertase, C4b2a, has been described more recently in patients with acute postinfectious glomerulonephritis or SLE. This factor is also an autoantibody of the IgG class that markedly prolongs the half-life of the convertase.[64]

The mechanism by which nephritic factor is formed as an autoantibody in these individuals is unknown. The significance of nephritic factor-mediated hypocomplementemia is clear, however. First, by permitting prolonged activation of the complement system, it may enhance tissue injury. Second, through depletion of C3 there may be defective complement-dependent opsonization of immune complexes. Third, if the process is severe enough, C3 can be markedly decreased, which increases the host's susceptibility to infection. Pyogenic infections, including meningitis, have occurred in these patients when the C3 level has been reduced to below about 10% of normal.[65,66]

Partial Lipodystrophy

Nephritic factor has also been demonstrated in patients with partial lipodystrophy who have not had nephritis. Of the 21 individuals with partial lipodystrophy reviewed in one study, 17 had depressed levels of C3 with normal levels of C4 and C2. Most of these 17 patients had detectable nephritic factor, and although 10 were clinically well, 7 had overt nephritis, especially membranoproliferative glomerulonephritis.[67] The relationship between the lipodystrophy and nephritic factor or between the nephritic factor and nephritis is not understood.

Acute Pancreatitis, Atheroembolic Disease, and Reaction to Radiographic Contrast Media

Some patients with acute pancreatitis develop respiratory distress syndrome. Profound complement activation can accompany pancreatitis, and complement split products have been implicated in the development of pulmonary sequelae.[68] Atheroembolic disease can be associated with hypocomplementemia, perhaps due to activity of enzymes of the coagulation system.[69] Intravenous injection of iodinated radiographic contrast medium can induce a rapid and significant cleavage of C3, perhaps through the alternative pathway, which could explain at least some of the reactions that occur in 5% to 8% of individuals who undergo this procedure.[70-72] Nonionic contrast media can inactivate C2 and activate the alternative pathway by interfering with the inhibitors I and H.[73]

C1 Inhibitor Deficiency With B-Cell Lymphoproliferative Disorder

Hereditary angioedema results from a genetic deficiency of the inhibitor of C1, the first component of the classical pathway. Due to defective hepatic synthesis of the inhibitor, the C1 enzyme is easily activated, producing a kininlike split product from C2 that acts directly on vascular smooth muscle to increase vascular permeability and cause the clinical signs of subcutaneous edema and laryngeal obstruction.

There are a small number of patients with an acquired form of C1-inhibitor deficiency, presenting as late-onset recurrent angioedema. These patients have normal synthesis and increased ca-

tabolism of C1-inhibitor, and decreased levels of C1q and C4. Not yet reported in the pediatric age group, this acquired C1-inhibitor deficiency syndrome has been described in patients with B-cell lymphoproliferative disorders such as B-cell lymphosarcoma, chronic lymphocytic leukemia, macroglobulinemia, multiple myeloma, and essential cryoglobulinemia.[74] Although B-cell malignancies have associated monoclonal immunoglobulins on their cell membranes, it does not seem that the immunoglobulins consume C1 or C1-inhibitor directly; this is shown clearly with B-cell clones producing IgA and IgD, neither of which fixes complement. In four patients it has been shown that an antibody develops to the unique components of the malignant B-cell clonal immunoglobulin.[75] The interaction between the anti-idiotypic antibodies and the patients' monoclonal immunoglobulins might be responsible for the increased consumption of C1q and consequent consumption of C1-inhibitor.

Hypocomplementemic Vasculitis Syndrome

A syndrome has been described in both adults and children of recurrent urticaria and angioedema, vasculitis with deposition of immunoglobulin and complement in the vessel wall, and depression of C1 through C5 (especially C1q), but normal levels of C1-inhibitor.[76,77] About half of the patients have had mild mesangial proliferative or membranoproliferative glomerulonephritis. The syndrome cannot be attributed to circulating immune complexes, and its pathogenesis is presently obscure. Corticosteroid treatment has been effective in some cases.[78]

Porphyria

In patients with erythropoietic protoporphyria or porphyria cutanea tarda, exposure of the skin to light of certain wavelengths activates complement, generating C5-derived chemotactic activity and reduced levels of serum C3 and C5.[79] Phototoxicity is associated clinically with blistering lesions and histologically with lysis of capillary endothelial cells, mast cell degranulation, and the appearance of neutrophils in the dermis, changes that can result from complement activation.[80] Interestingly, sera from patients with porphyria cutanea tarda show complement activation and the capacity to stimulate leukocyte chemotaxis activation when irradiated with light of certain spectra, and porphyrins added to normal serum will cause complement consumption when similarly light exposed.[80] The clinical disease may be mediated by porphyrins in skin absorbing light energy and transferring this energy to form oxygen radicals, setting up tissue oxidation and complement activation.

SECONDARY DISORDERS OF COMPLEMENT DUE PRIMARILY TO DECREASED SYNTHESIS

The Newborn

The newborn state is the most common condition associated with complement deficiency. Cord serum was reported to have subnormal complement activity in 1927,[81] and all studies published since then have confirmed this finding.[82] In term infants, activity of the classical pathway, measured as CH_{50}, has been found to be approximately 75% of normal adult values. Preterm infants had even lower values (58% of adult levels).[83-85] The alternative pathway has been more abnormal, with 56% of adult activity.[82,83,85-87] All individual components of either pathway that have been measured have been mildly to moderately decreased.

Other studies have shown that one half of term infants have decreased classical pathway opsonization of group B streptococci,[82] with one third having decreased alternative pathway opsonization of pneumococci, endotoxin, or *Escherichia coli*.[83,88,89] Complement levels reach the adult range by 3 to 6 months of age, with the exception of C1q and properdin, which can be low until 12 to 18 months of age.[90,91]

However the data are analyzed, the newborn infant displays a deficiency in complement function relative to a normal adult. The degree of deficiency is such that it probably would not predispose a normal adult to infection. However, it seems likely that the deficiency of multiple components and of both pathways found in neonates, especially in conjunction with the decreased phagocyte function known to exist in that population, does increase their likelihood of serious infection. In the presence of high levels of transferred maternal antibody, the relatively mild deficiency of classical pathway function might not be detrimental. In the absence of such antibody, however, the alternative pathway probably would offer inadequate protection against a large inoculum of microorganisms in a majority of newborn infants. With this configuration of abnormalities, infections due to extracellular bacteria would be predicted, and, in fact, these organisms are particularly troublesome to the neonate. These considerations remain to be proved, however.

Malnutrition and Anorexia Nervosa

Patients with malnutrition or anorexia nervosa may have significant depletion of components and decreased functional activity of complement.[92-95] Both classical and alternative pathways can be deficient. Although synthesis of components is depressed in these conditions, serum from some patients with malnutrition also appears to contain immune complexes and endotoxin, which could accelerate depletion.[95,96]

Liver Cirrhosis, Reye's Syndrome, and Hepatic Failure

Severe chronic cirrhosis of the liver or fulminant hepatic failure can result in decreased complement levels, especially decreased C3.[97-99] Decreased synthesis of C3 has been documented in some patients. Some patients with severe hepatic failure have developed meningococcal infections associated with decreased complement synthesis. This suggests that secondary complement deficiency may contribute to susceptibility to infection in patients with fulminant hepatic disease.[49] Individuals with Reye's syndrome can have marked deficiency of complement components.[100,101] Some of these patients have circulating immune complexes, and their deficiencies may be due, at least in part, to activation and consumption of C3.

SECONDARY DISORDERS OF COMPLEMENT ASSOCIATED WITH INCREASED CATABOLISM

Nephrotic Syndrome

Children with nephrotic syndrome are at increased risk for serious bacterial infection. Serum levels of C3, C4, and properdin have been slightly decreased or normal in these children. Factor B has been commonly deficient and this deficiency has been associated with de-

fective opsonization of *E coli* or zymosan.[102,103] In one study, there was a strong correlation between serum factor B and serum albumin concentrations, suggesting that factor B (molecular weight, 100 000) was being lost in the urine.[103]

Increased C1q Catabolism Associated With Hypogammaglobulinemia

Patients with hypogammaglobulinemia have a variable decrease in serum concentrations of C1q, which is proportional to the decrease in IgG.[104,105] Immunoglobulin G normally interacts with C1q in serum and protects it from increased catabolism. In agreement with this, infusion of IgG in hypogammaglobulinemic patients will reverse the complement deficiency.[104]

COMPLEMENT ABNORMALITIES SECONDARY TO DEFICIENCY OF NONCOMPLEMENT SERUM OR MEMBRANE PROTEINS

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is associated with multiple membrane defects, making variable proportions of erythrocytes abnormally sensitive to complement-mediated cell injury.[106-108] The erythrocytes have greater than normal avidity for C3 and increased sensitivity to cell lysis by binding of the MAC. These cells have an acquired deficiency of a membrane control protein, "decay accelerating factor" (DAF), as well as a deficiency in "homologous restriction protein," also known as C8-binding protein.

Studies have shown DAF to be a membrane-associated protein found not only on erythrocytes but also on granulocytes, monocytes, lymphocytes, platelets, vascular epithelium, extravascular epithelial and secretory cells, and in soluble form in saliva and tears.[109-112] Decay accelerating factor normally inhibits the assembly of C3-cleaving enzymes ($\overline{C4b2a}$ and $\overline{C3bBb}$) and blocks the amplification steps of both the classical and alternative pathways.[108,113] In the absence of DAF, there is increased activity of C3b on the cell surface generating MACs (C5b-9) and cell lysis.

Homologous restriction protein normally binds C8 and C9, limiting formation of the MAC. Paroxysmal nocturnal hemoglobinuria cells deficient in this protein have decreased ability to restrict insertion or fixation of C5b-9, and are more easily lysed.[114,115]

Studies of genomic material of PNH affected and normal cells have not revealed DAF gene or mRNA alterations.[116] Both DAF and acetylcholinesterase, another protein missing on PNH erythrocytes, are members of a family of membrane proteins linked to the cell membrane by a phospholipid structure.[117] It is likely that PNH is due to defective insertion of anchoring structures into the cell membrane due to a clonal somatic mutation.

Decreased Alternative Pathway Function Associated With Hypogammaglobulinemia, β-Thalassemia Major, or Splenectomy

The alternative complement pathway can be activated in the absence of specific antibody by a variety of surfaces that provide a microenvironment in which the alternative pathway C3 convertase is relatively protected against inactivation. A large body of experimental data indicates that antibody to the surface can enhance alternative pathway activation.[118-121] Serum from patients with hypogammaglobulinemia functions defectively in the alternative pathway, and this defect was shown to disappear after administration of immunoglobulin.[120,121] Serum from about 20% of patients with β-thalassemia major and about 10% of patients with splenectomy has been found to be deficient in alternative pathway activity.[122] The basis for the deficiency in these patients is not known.

CONCLUSION

There are a large number of disease states in which secondary disorders of complement have been recognized. Most of these abnormalities may be screened for by serum determinations of CH_{50}. Specific components can be measured with antibody and may suggest what has caused a deficiency or activation of the system. New tests that more sensitively measure complement activation[123,124] may be more useful in assessing disease activity and may lead to an improved understanding of how complement mediates human disease.

References

1. Altenburger KM, Johnston RB Jr. The complement system and its disorders in man. In: Chandra RK, ed. *Primary and Secondary Immunodeficiency Disorders*. Edinburgh, Scotland: Churchill Livingstone Inc; 1983:113.
2. Frank MM. Complement in the pathophysiology of human disease. *N Engl J Med*. 1987; 316:1525-1530.
3. Guenther LC. Inherited disorders of complement. *J Am Acad Dermatol*. 1983;9:815-839.
4. Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of Neisserial and other infections in an immune deficiency. *Medicine*. 1984;63:243-273.
5. Müller-Eberhard HJ. Chemistry and function of the complement system. In: Dixon FJ, Fisher DW, eds. *The Biology of Immunologic Disease*. Sunderland, Mass: Sinauer Associates; 1983:129-138.
6. Fearon DT. Complement. *J Allergy Clin Immunol*. 1983;71:520-529.
7. Schur PH. Complement in lupus. *Clin Rheumatol Dis*. 1975;1:519-543.
8. Schifferli JA, Ng YC, Peters DK. The role of complement and its receptor in the elimination of immune complexes. *N Engl J Med*. 1986;315: 488-495.
9. Biesecker G, Lavin L, Ziskind M, Koffler D. Cutaneous localization of the membrane attack complex in discoid and systemic lupus erythematosus. *N Engl J Med*. 1982;306:264-270.
10. Biescker G, Katz S, Koffler D. Renal localization of the membrane attack complex in systemic lupus erythematosus nephritis. *J Exp Med*. 1981;154:1779-1794.
11. Falk RJ, Dalmasso AP, Kim Y, Lam S, Michael A. Radioimmunoassay of the attack complex of complement in serum from patients with systemic lupus erythematosus. *N Engl J Med*. 1985;312:1597-1599.
12. Wilson JF, Wong WW, Schur PH, Fearon DT. Mode of inheritance of decreased C3b receptors on erythrocytes of patients with systemic lupus erythematosus. *N Engl J Med*. 1982;302:981-986.
13. Ross GD, Young WF, Walport MJ, et al. Disease-associated loss of erythrocyte complement receptors (CR1, C3b receptors) in patients with systemic lupus erythematosus and other diseases involving autoantibodies and/or complement activation. *J Immunol*. 1985;135:2005-2014.
14. Wilson JG, Jack RM, Wong WW, Fearon DT. Autoantibody to the C3b/C4b receptor and absence of this receptor from erythrocytes of a patient with systemic lupus erythematosus. *J Clin Invest*. 1985;76:182-190.
15. Alpert E, Isselbacher KJ, Schur PH. The pathogenesis of arthritis associated with viral hepatitis: complement-component studies. *N Engl J Med*. 1971;285:185-189.
16. Breedveld FC, Fibbe WE, Hermans J, Vander-Meer JW, Cats A. Factors influencing the incidence of infections in Felty's syndrome. *Arch Intern Med*. 1987;147:915-920.
17. Dobrin RS, Day NK, Quie PG, et al. The role of complement, immunoglobulin and bacterial antigen in coagulase-negative staphylococcal shunt nephritis. *Am J Med*. 1975;59:660-673.
18. Jones EA, Frank MM, Jaffe CJ, Vierling JM. Primary biliary cirrhosis and the complement system. *Ann Intern Med*. 1979;90:72-84.
19. Lachmann PJ, Peters DK. Complement. In: Lachmann PJ, Peters DK, eds. *Clinical Aspects of Immunology*. 4th ed. Oxford, England: Blackwell Scientific Publications Inc; 1982:18-49.
20. Lawley TJ, Bielory L, Gascon P, et al. A prospective clinical and immunologic analysis of patients with serum sickness. *N Engl J Med*. 1984;311:1407-1413.

21. Perrin LH, Lambert PH, Nydegger UE, Meischer PA. Quantitation of C3PB (properdin factor B) and other complement components in diseases associated with a low C3 level. *Clin Immunol Immunopathol.* 1973;2:1627.

22. Nydegger UE, Zubler RH, Gabay R, et al. Circulating complement breakdown products in patients with rheumatoid arthritis: correlation between plasma C3d, circulating immune complexes, and clinical activity. *J Clin Invest.* 1977;59:862-868.

23. Mohammed I, Holborow EJ, Fry L, Thompson BR, Hoffbrand AV, Steward JS. Multiple immune complexes and hypocomplementaemia in dermatitis herpetiformis and coeliac disease. *Lancet.* 1976;2:487-490.

24. Pearson HA, Spencer RP, Cornelius EA. Functional asplenia in sickle-cell anemia. *N Engl J Med.* 1969;281:923-926.

25. Johnston RB Jr, Newman SL, Struth AG. An abnormality of the alternate pathway of complement activation in sickle-cell disease. *N Engl J Med.* 1973;288:803-808.

26. Winkelstein JA, Drachman RH. Deficiency of pneumococcal serum opsonizing activity in sickle-cell disease. *N Engl J Med.* 1968:279:459-466.

27. Wilson WA. Nature of complement deficiency in sickle cell disease. *Arch Dis Child.* 1983;58:235-236.

28. Bjornsen AB, Lobel JS. Direct evidence that decreased serum opsonization of *Streptococcus pneumoniae* via the alternative complement pathway in sickle cell disease is related to antibody deficiency. *J Clin Invest.* 1987;79:388-398.

29. De Ceulaer K, Forbes M, Maude GH, Pagliccua A, Serjeant GR. Complement and immunoglobulin levels in early childhood in homozygous sickle cell disease. *J Clin Immunol.* 1986;21:37-41.

30. Chudwin DS, Korenblit AD, Kingzette M, Artrip S, Rao S. Increased activation of the alternative complement pathway in sickle cell disease. *Clin Immunol Immunopathol.* 1985;37:93-97.

31. Poskitt TR, Fortwengler HP Jr, Lunskis BJ. Activation of the alternate complement pathway by autologous red cell stroma. *J Exp Med.* 1973;138:715-722.

32. De Ceulaer K, Wilson WA, Morgan AG, Serjeant GR. Plasma haemoglobin and complement activation in sickle cell disease. *J Clin Lab Immunol.* 1981;6:57-60.

33. Chenowith DE, Cooper SW, Hugli TE, Stewart RW, Blackstone EH, Kirklin JW. Complement activation during cardiopulmonary bypass: evidence for generation of C3a and C5a anaphylatoxins. *N Engl J Med.* 1981;304:497-503.

34. Hakim RM, Breillatt J, Lazarus JM, Port FK. Complement activation and hypersensitivity reactions to dialysis membranes. *N Engl J Med.* 1984;311:878-882.

35. Hammerschmidt DE, Craddock PR, McCullough J, Kronenberg RS, Dalmasso AP, Jacob HS. Complement activation and pulmonary leukostasis during nylon fiber filtration leukapheresis. *Blood.* 1978;51:721-730.

36. Salama A, Hugo F, Heinrich D, et al. Deposition of terminal C5b-9 complement complexes on erythrocytes and leukocytes during cardiopulmonary bypass. *N Engl J Med.* 1988;318:408-414.

37. Nusbacher J, Rosenfeld SI, MacPherson JL, Thiem PA, Leddy JP. Nylon fiber leukapheresis: associated complement component changes and granulocytopenia. *Blood.* 1978;51:359-365.

38. Fearon DT, Ruddy S, Schur PH, McCabe WR. Activation of the properdin pathway of complement in patients with gram-negative bacteremia. *N Engl J Med.* 1975;191:937-940.

39. Kalter ES, Daha MR, ten Cate JW, Verhoef J, Bouma BN. Activation and inhibition of Hageman factor-dependent pathways and the complement system in uncomplicated bacteremia or bacterial shock. *J Infect Dis.* 1985;151;1019-1027.

40. Palestine AG, Klemperer MR. In vivo activation of properdin factor B in normotensive bacteremic individuals. *J Immunol.* 1976;117:703-705.

41. Reed WP, Davidson MS, Williams RC Jr. Complement system in pneumococcal infections. *Infect Immunol.* 1976;13:1120-1125.

42. Macher AM, Bennett JE, Gadek JE, Frank MM. Complement depletion in cryptococcal sepsis. *J Immunol.* 1978;120:1686-1690.

43. Mayes JT, Schreiber RD, Cooper NR. Development and application of an enzyme-linked immunosorbent assay for the quantitation of alternative complement pathway activation in human serum. *J Clin Invest.* 1984;73:160-170.

44. Quinn PH, Crosson FJ Jr, Winkelstein JA, Moxon ER. Activation of the alternative complement pathway of *Haemophilus influenzae* type B. *Infect Immunol.* 1977;16:400-402.

45. McSharry JJ, Pickering RJ, Caliguiri LA. Activation of the alternative complement pathway by enveloped viruses containing limited amounts of sialic acid. *Virology.* 1981;114:507-515.

46. Bokisch VA, Top FH, Russell PK, Dixon FJ, Mueller-Eberhard EJ. The potential pathogenic role of complement in dengue hemorrhagic shock syndrome. *N Engl J Med.* 1973;289:996-1000.

47. de Bracco MME, Rimoldi MT, Cossio PM, et al. Argentine hemorrhagic fever: alterations of the complement system and anti-Junin-virus humoral response. *N Engl J Med.* 1978;299:216-221.

48. Neva FA, Howard WA, Glew RH, et al. Relationship of serum complement levels to events of the malarial paroxysm. *J Clin Invest.* 1974;54:451-460.

49. Ellison RT, Mason SR, Kohler PF, Curd JG, Reller LB. Meningococcemia and acquired complement deficiency: association with hepatic failure. *Arch Intern Med.* 1986;146:1539-1540.

50. Ammann AJ, Abrams D, Conant D, et al. Acquired immune dysfunction in homosexual men: immunologic profiles. *Clin Immunol Immunopathol.* 1983;27:315-325.

51. Tausk FA, McCutchan JA, Spechko P, Schrieber RD, Gigli I. Altered erythrocyte C3b receptor expression, immune complexes and complement activation in homosexual men in varying risk groups for acquired immune deficiency syndrome. *J Clin Invest.* 1986;78:977-982.

52. Gelfand JA, Donelan M, Hawiger A, Burke JF. Alternative complement pathway activation increases mortality in a model of burn injury in mice. *J Clin Invest.* 1982;70:1170-1176.

53. Hammerschmidt DE, Weaver LJ, Hudson LD, Craddock PR, Jacob HS. Association of complement activation and elevated plasma-C5a with adult respiratory distress syndrome: pathophysiological relevance and possible prognostic value. *Lancet.* 1980;1:947-949.

54. Till GO, Ward PA. Systemic complement activation and acute lung injury. *Fed Proc.* 1986;45:13-18.

55. Davis CF, Moore FD, Rodrick ML, Fearon DT, Mannick JA. Neutrophil activation after burn injury: contributions of the classic complement pathway and of endotoxin. *Surgery.* 1987;102:477-484.

56. Davis JM, Dineen P, Gallin JL. Neutrophil degranulation and abnormal chemotaxis after thermal injury. *J Immunol.* 1980;124:1467-1471.

57. Hallgreen R, Samuelsson T, Modig J. Complement activation and increased alveolar capillary permeability after major surgery and in adult respiratory distress syndrome. *Crit Care Med.* 1987;15:189-193.

58. Sprung CL, Schultz DR, Marcial E, et al. Complement activation in septic shock patients. *Crit Care Med.* 1986;14:525-528.

59. Zilow G, Geiger U, Kirschfin M, Rother U, Joka T. C3a as a prognostic indicator for the development of adult respiratory distress syndrome (ARDS) in polytrauma patients. *Immunobiology.* 1986;173:475.

60. Hammerschmidt DE. Clinical utility of complement anaphylatoxin assays. *Complement.* 1986;3:166-176.

61. Gotoff SP, Fellers FX, Vawter GF, Janeway CA, Rosen FS. The $beta_{1c}$ globulin in childhood nephrotic syndrome: laboratory diagnosis of progressive glomerulonephritis. *N Engl J Med.* 1965;273:524-529.

62. West CD, McAdams AJ, McConville JM, Davis NC, Holland NH. Hypocomplementemic and normocomplementemic persistent (chronic) glomerulonephritis; clinical and pathologic characteristics. *J Pediatr.* 1965;67:1089-1112.

63. Spitzer RE, Vallota EH, Forristal J, et al. Serum C3 lytic system in patients with glomerulonephritis. *Science.* 1969;164:436-437.

64. Halbwachs L, Leveille M, Lesavre P, et al. Nephritic factor of the classical pathway of complement: immunoglobulin G autoantibody directed against the classical pathway C3 convertase enzyme. *J Clin Invest.* 1980;65:1249-1256.

65. Edwards KM, Alford R, Gewurz H, Mold C. Recurrent bacterial infections associated with C3 nephritic factor and hypocomplementemia. *N Engl J Med.* 1983;308:1138-1141.

66. Thompson RA, Yap PL, Brettle RB, Dunmore RE, Chapel H. Meningococcal meningitis associated with persistent hypocomplementaemia due to circulating C3 nephritic factor. *Clin Exp Immunol.* 1983;52:153-156.

67. Sissons JGP, West RJ, Fallows J, et al. The complement abnormalities of lipodystrophy. *N Engl J Med.* 1976;294:461-465.

68. Horn JK, Ranson JHC, Goldstein IM, et al. Evidence of complement catabolism in experimental acute pancreatitis. *Am J Pathol.* 1980;101:205-216.

69. Cosio FG, Zager RA, Sharma HM. Atheroembolic renal disease causes hypocomplementaemia. *Lancet.* 1985;2:118-121.

70. Arroyave CM, Tan EM. Mechanism of complement activation by radiographic contrast media. *Clin Exp Immunol.* 1977;29:89-94.

71. Kolb WP, Lang JH, Lasser EC. Nonimmunologic complement activation in normal human serum induced by radiographic contrast media. *J Immunol.* 1978;121:1232-1238.

72. Von Zabern I, Przykleuk H, Vogt W, Sachsenheimer W. Effect of radiographic contrast media on complement components C3 and C4: generation of C3b-like C3 and C4b-like C4. *Int J Immunopharmacol.* 1983;5:503-514.

73. Von Zabern I, Przykleuk H, Nolte R, Vogt W. Effect of metrizamide, a nonionic radiographic contrast agent, on human serum complement: comparison with ionic contrast media. *Int Arch Allergy Appl Immunol.* 1984;73:321-329.

74. Sheffer AL, Austen KF, Rosen FS, Fearon DT. Acquired deficiency of the inhibitor of the first component of complement: report of five additional cases with commentary on the syndrome. *J Allergy Clin Immunol.* 1985;75:640-646.

75. Geha RS, Quinti I, Austen KF, Cicardi M, Sheffer A, Rosen FS. Acquired C1-inhibitor deficiency associated with anti-idiotypic antibody to monoclonal immunoglobulins. *N Engl J Med.* 1985;312:534-540.

76. Marder RJ, Potempa LA, Jones JV, Torlumi D, Schmid FR, Gewurz H. Assay, purification and further characterization of 75 C1q-precipitins (C1q-p) in hypocomplementemic vasculitis urticaria syndrome and systemic lupus erythematosus. *Acta Pathol Microbiol Immunol Scand.* 1984;284 (suppl):25-34.

77. Waldo FB, Leist PA, Strife CF, Forristal J, West CD. Atypical hypocomplementemic vasculitis syndrome in a child. *J Pediatr.* 1985;106:745-750.

78. Geha RS, Aki KF. Skin lesions angioedema, eosinophilia, and hypocomplementemia. *J Pediatr.* 1976:89:724-727.

79. Lim HW, Poh-Fitzpatrick MB, Gigli I. Activation of the complement system in patients with

porphyrias after irradiation in vivo. *J Clin Invest.* 1984;74:1961-1965.

80. Lim HW, Perez HD, Poh-Fitzpatrick M, Goldstein IM, Gigli I. Generation of chemotactic activity in serum from patients with erythropoietic protoporphyria and porphyria cutanea tarda. *N Engl J Med.* 1981;304:212-216.

81. Nattan-Larrier L, Lepine P, May J. Dosage comparatif de l'alexine dans le sang de la mère et dans le sang de l'enfant au moment de la naissance. *C R Soc Biol.* 1927;97:671-672.

82. Johnston RB Jr, Altenburger KM, Atkinson AW Jr, Curry RH. Complement in the newborn infant. *Pediatrics.* 1979;64:781-786.

83. Notarengelo LD, Chirico G, Chiara A, et al. Activity of classical and alternative pathways of complement in preterm and small for gestational age infants. *Pediatr Res.* 1984;18:281-285.

84. Sawyer MK, Forman ML, Kuplic LS, Stiehm ER. Developmental aspects of the human complement system. *Biol Neonate.* 1971;19:148-162.

85. Strunk RC, Fenton LJ, Gaines. Alternative pathway of complement activation in fullterm and premature infants. *Pediatr Res.* 1979;13:641-643.

86. Adamkin D, Stitzel A, Urmson J, Farnett ML, Post E, Spitzer R. Activity of the alternative pathway of complement in the newborn infant. *J Pediatr.* 1978;93:604-608.

87. Shapiro R, Beatty DW, Woods DL, Malan AF. Serum complement and immunoglobulin values in small-for-gestational-age infants. *J Pediatr.* 1981;99:139-141.

88. Mills EL, Bjorksten B, Quie PG. Deficient alternative complement pathway activity in newborn sera. *Pediatr Res.* 1979;13:1341-1344.

89. Stossel TP, Alper CA, Rosen FS. Opsonic activity in the newborn: role of properdin. *Pediatrics.* 1973;52:134-137.

90. Davis CA, Vallota EH, Forristal J. Serum complement levels in infancy: age related changes. *Pediatr Res.* 1979;13:1043-1046.

91. Fireman P, Zuchowski DA, Taylor PM. Development of human complement system. *J Immunol.* 1969;103:25-31.

92. Keusch GT, Torun B, Johnston RB Jr, Urrutia JJ. Impairment of hemolytic complement activation by both classical and alternative pathways in serum from patients with kwashiorkor. *J Pediatr.* 1984;105:434:436.

93. Kim Y, Michael AF. Hypocomplementemia in anorexia nervosa. *J Pediatr.* 1975;87:582-585.

94. Sirisinha S, Suskind RM, Edelman R, Kulapongs P, Olson RE. The complement system in protein-calorie malnutrition--a review. In: Suskind RM, ed. *Malnutrition and the Immune Response.* New York, NY: Raven Press; 1977:309-320.

95. Suskind R, Edelman R, Kulapongs P, Olson RE. Complement activity in children with protein-calorie malnutrition. *Am J Clin Nutr.* 1976;29:1089-1092.

96. Klein K, Suskind RM, Kulapongs P, Mertz G, Olson RE. Endotoxemia, a possible cause of decreased complement activity in malnourished Thai children. In: Suskind RM, ed. *Malnutrition and the Immune Response.* New York, NY: Raven Press Inc; 1977:321-328.

97. Larcher VF, Wyke RJ, Vergani D, Mowat AP, William SR. Yeast opsonization and complement in children with liver disease: analysis of 69 cases. *Pediatr Res.* 1983;17:296-300.

98. Larcher VF, Manolaki N, Vegnente A, Mowat AP. Spontaneous bacterial peritonitis in children with chronic liver disease: clinical features and etiologic factors. *J Pediatr.* 1985;106:907-912.

99. Petz L. Variable mechanisms for low serum-complement in liver disease. *Lancet.* 1971;2:1033-1034.

100. Marder HK, Strife CF, Forristal J, Partin J. Hypocomplementemia in Reye syndrome: relationship to disease stage, circulating immune complexes, and C3b amplification loop protein synthesis. *Pediatr Res.* 1981;15:362-365.

101. Pickering RJ, Urizar RE, Hanson PA, Laffin RJ. Abnormalities of the complement system in Reye syndrome. *J Pediatr.* 1979;94:218-222.

102. Anderson DC, York TL, Rose G, Smith CW. Assessment of serum factor B, serum opsonins, granulocyte chemotaxis, and infection in nephrotic syndrome of children. *J Infect Dis.* 1979;140:1-11.

103. McLean RH, Forsgren A, Bjorkstein B, Kim Y, Quie PG, Michael AF. Decreased serum factor B concentration associated with decreased opsonization of *Escherichia coli* in the idiopathic nephrotic syndrome. *Pediatr Res.* 1977;11:910-916.

104. Atkinson JP, Fisher RI, Reinhardt, Frank MM. Reduced concentrations of the first component of complement in hypogammaglobulinemia: correction by infusion of gamma-globulin. *Clin Immunol Immunopathol.* 1978;9:350-355.

105. Kohler PF, Muller-Eberhard HJ. Metabolism of human C1q: studies in hypogammaglobulinemia, myeloma, and systemic lupus erythematosus. *J Clin Invest.* 1972;51:868-875.

106. Nicholson-Weller A, March JP, Rosenfeld, SI, Austen KF. Affected erythrocytes of patients with paroxysmal nocturnal hemoglobinuria are deficient in the complement regulatory protein, decay accelerating factor. *Proc Natl Acad Sci USA.* 1983;80:5066-5070.

107. Pangburn MK, Schreiber RD, Muller-Eberhard HJ. Deficiency of an erythrocyte membrane protein with complement regulatory activity in paroxysmal nocturnal hemoglobinuria. *Proc Natl Acad Sci USA.* 1983;80:5430-5434.

108. Rosse WF. The control of complement activation by the blood cells in paroxysmal nocturnal hemoglobinuria. *Blood.* 1986;67:268-269.

109. Asch AS, Kinoshita EA, Jaffe A, Nussenzweig V. Decay accelerating factor is present in cultured human umbilical vein endothelial cells. *J Exp Med.* 1986;163:221-226.

110. Kinoshita T, Medof ME, Silber R, Nussenzweig V. Distribution of decay-accelerating factor in the peripheral blood of normal individuals and patients with paroxysmal nocturnal hemoglobinuria. *J Exp Med.* 1985;162:75-92.

111. Medof ME, Walter EI, Rutgers JL, Knowles DM, Nussenzweig V. Identification of the complement decay accelerating factor (DAF) on epithelium and glandular cells and in body fluids. *J Exp Med.* 1987;165:848-854.

112. Nicholson-Weller A, March JP, Rosen CE, Spicer DB, Austen KF. Surface membrane expression by human blood leucocytes and platelets of decay accelerating factor, a regulatory protein of the complement system. *Blood.* 1985;65:1237-1244.

113. Medof ME, Kinoshita T, Nussenzweig V. Inhibition of complement activation on the surface of cells after incorporation of decay-accelerating factor (DAF) into their membranes. *J Exp Med.* 1984;160:1558-1578.

114. Hansch GM, Schonermark S, Roekke D. Paroxysmal nocturnal hemoglobinuria type III: lack of an erythrocyte membrane protein restricting the lysis by C5b-9. *J Clin Invest.* 1987;80:7-12.

115. Parker CJ, Weidmer T, Sims PJ, Rosse WF. Characterization of the complement sensitivity of paroxysmal nocturnal hemoglobinuria erythrocytes. *J Clin Invest.* 1985;75:2074-2084.

116. Stafford HA, Tykocinski ML, Lublin DM, et al. Normal polymorphic variations and transcription of the decay accelerating factor gene in paroxysmal nocturnal hemoglobinuria cells. *Proc Natl Acad Sci USA.* 1988;85:880-884.

117. Medof ME, Gottlieb A, Kinoshita T, et al. Relationship between decay accelerating factor deficiency, diminished acetylcholinesterase activity, and defective terminal complement pathway restriction in paroxysmal nocturnal hemoglobinuria erythrocytes. *J Clin Invest.* 1987;80:165-174.

118. Fries LF, Gaither TA, Hammer CH, Frank MM. C3b covalently bound to IgG demonstrates a reduced rate of inactivation by factors H and I. *J Exp Med.* 1984;160:1640-1655.

119. Ratnoff WD, Fearon DT, Austen KF, et al. The role of antibody in the activation of the alternative complement pathway. *Springer Semin Immunopathol.* 1983;6:361-371.

120. Corry JM, Polhill RB Jr, Edmonds SR, Johnston RB Jr. Activity of the alternative complement pathway after splenectomy: comparison to activity in sickle cell disease and hypogammaglobulinemia. *J Pediatr.* 1979;95:964-969.

121. Polhill RB Jr, Newman SL, Pruitt KM, Johnston RB Jr. Kinetic assessment of alternative complement pathway activity in a hemolytic system, II: influence of antibody on alternative pathway activation. *J Immunol.* 1978;121:371-376.

122. Corry JM, Marshall WC, Guthrie LA, Peerless AG, Johnston RB Jr. Deficient activity of the alternative pathway of complement in β-thalassemia major. *AJDC.* 1981;135:529-531.

123. Burger R, Zilow G, Bader A, Freidlein A, Naser W. The C terminus of the anaphylatoxin C3a generated upon complement activation represents a neoantigenic determinant with diagnostic potential. *J Immunol.* 1988;141:553-558.

124. Koski CL, Sanders ME, Swoveland PT, et al. Activation of terminal components of complement in patients with Guillain-Barre syndrome and other demyelinating neuropathies. *J Clin Invest.* 1987;80:1492-1497.

AJDC Is Moving . . .

The AJDC editorial office is now located at Tulane University. Please address all correspondence, manuscripts, and inquiries to Vincent A. Fulginiti, MD, Editor, *AJDC*, Dean's Office, Room 1529, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; (504) 584-1989.

When their recipe calls for allergy relief the twins take Tavist® Syrup

Tavist® Syrup contains the right ingredient to relieve allergies and keep the twins in the kitchen. One dose provides up to 12 hours of effective relief from symptoms of allergic rhinitis and mild urticaria.

Tavist® Syrup also has a convenient b.i.d. dosage to aid compliance, and a pleasant citrus taste even these master chefs can appreciate.

Prescribe the liquid allergy medicine that Pediatricians prescribe more than any other.* Prescribe Tavist® Syrup.

Tavist® Syrup. Lets kids be kids 12 hours long

(clemastine fumarate) 0.67mg/5ml

© 1989 Sandoz Pharmaceuticals Corporation

*National Prescription Audit, IMS America, LTD. Data on file, Sandoz Pharmaceuticals Corporation

Please see following page for brief summary of prescribing information.

TAS-489-2

BRIEF SUMMARY

TAVIST®

(clemastine fumarate) SYRUP 0.5 mg/5 ml
(present as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

Tavist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see *DOSAGE AND ADMINISTRATION*).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see *PRECAUTIONS — Drug Interactions* in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see *PRECAUTIONS — Nursing Mothers* in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist® (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (6 mg clemastine).

For Urticaria and Angioedema — The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED

Tavist® (clemastine fumarate) Syrup

Clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

[TAS-Z3 APRIL 1, 1986]

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

PEDIATRICIANS

Infectious Disease

ARAMCO's Dhahran Health Center (DHC) in Saudi Arabia needs a Pediatric Infectious Disease Specialist to join a staff of 17 in its modern 483 bed hospital. The DHC functions as a referral center for a patient population of approximately 200,000 and the medical problems encountered are varied and challenging. It has the latest medical equipment and special care units including an 8 bed Pediatric ICU and a 28 bed Immediate Care ICU.

American Board Certification in Pediatrics and 2 years after residency required. Board Certification in subspecialty preferred.

Employment with ARAMCO will provide you with an interesting lifestyle in a multicultural environment, including comfortable family living arrangements, free medical care while in Saudi Arabia, fine schools and a broad spectrum of recreational opportunities, plus 36 days of vacation annually, allowing for extensive travel. We provide an attractive compensation package which includes an expatriate premium.

For immediate consideration, **CALL OUR 24 HOUR, 7 DAYS PER WEEK TOLL-FREE NUMBER 1-800-221-3333, EXT. R11,** or send resume to: **RES-R11, 7676 Hillmont, Suite 290, Dept. 06G-012-9, Houston, Texas 77040.**

ARAMCO

Transient Erythroblastopenia of Childhood

A Review of 26 Cases and Reassessment of Indications for Bone Marrow Aspiration

Taru Hays, MD; Peter A. Lane, Jr, MD; Frank Shafer, MD

• **Clinical and hematological presentations of 26 consecutive patients with transient erythroblastopenia of childhood diagnosed during July 1979 to September 1986 were compared with 26 patients with acute leukemia who presented with anemia and a normal platelet count. It was easy to distinguish acute leukemia from transient erythroblastopenia of childhood on a clinical and laboratory basis. In most cases, bone marrow examination was not necessary.**

(*AJDC*. 1989;143:605-607)

Transient erythroblastopenia of childhood (TEC) is a normocytic, normochromic anemia that occurs in previously normal infants and young children.[1-11] Transient erythroblastopenia of childhood is generally classified as a pure red blood cell aplasia, because the disorder is characterized by reticulocytopenia in the blood and erythroid hypoplasia in the bone marrow. Platelet counts in affected children are always normal or elevated. However, significant neutropenia occurs in some cases. Five of 24 patients recently described by Glader[11] had absolute neutrophil counts less than 1.0×10^9/L. In one case, the neutrophil count was only 0.2×10^9/L.[10]

The diagnosis of TEC is typically made by excluding the congenital hypoplastic anemia of Diamond and Blackfan[10-12] and other disorders associated with red cell aplasia, such as congenital hemolytic anemias, renal disease, hypothyroidism, and malnutrition. Although bone marrow aspiration is rarely helpful in differentiating TEC from these disorders, the procedure is frequently recommended for children with red cell aplasia to definitely exclude the possibility of malignancy.

We retrospectively reviewed 26 cases of TEC to further define its clinical spectrum. We also contrast the clinical presentation of TEC with that of 288 consecutive cases of acute leukemia (AL) observed during the same period in an attempt to assess the value of bone marrow aspiration for children with presumed TEC.

PATIENTS AND METHODS

Twenty-six consecutive cases of TEC, diagnosed and followed up at the Denver (Colo) Children's Hospital over a 7-year period (July 1979 to September 1986) were retrospectively reviewed. All 26 had been clinically evaluated by one of us (T.H.). All of the children had been well previously, having no historical or physical evidence of chronic disease, severe failure to thrive, congenital anomalies, previous anemias, jaundice, sepsis, recent surgical procedures, renal disease, or exposure to toxins or drugs associated with bone marrow suppression. Complete blood cell (Coulter S + 2), manual white blood cell differential, platelet, and corrected reticulocyte counts (corrected to a hemoglobin level of 120 g/L) were available for all patients. Bone marrow aspiration had been performed in 21 patients.

The case records of all patients with AL diagnosed during the same period at the same institution were also reviewed. Twenty-six leukemic children showed normal platelet counts at diagnosis, and the clinical features of these patients were recorded for comparison with patients with TEC.

The age distribution of the patients with TEC at diagnosis was 6 to 30 months. There were 16 girls and 10 boys. Eighteen of the 26 patients presented because of parental concerns about pallor. Twelve patients had a history of a preceding viral illness within 6 weeks of the diagnosis. Ten had had upper respiratory tract infections and 4 had had symptoms of gastroenteritis. Other complaints included irritability or decrease in activity in 5 patients, and weight loss with decreased appetite in 4 patients. Two patients were referred to our center after a blood count was obtained during work-up of unrelated symptoms; 1, during an evaluation of seizures; and 1, during an emergency room visit for head trauma. One patient presented with a history of fainting spells. Physical examination results showed pallor in all 26 patients with TEC, but without significant lymphadenopathy or hepatosplenomegaly. Patients with more severe anemia also demonstrated signs of increased cardiac output with tachycardia and a systolic murmur.

RESULTS

Some of the initial laboratory data from children with TEC are summarized in Fig 1.[1] Hemoglobin values ranged from 39 to 90 g/L (mean, 69 g/L) with a mean corpuscular volume (MCV) of 73 to 89.5 fL (mean, 81.4 fL). Of the three patients with high MCVs,[13] two had MCVs of 86 fL and one had an MCV of 89.5 fL. This latter patient's blood smear showed rouleaux, which may have falsely elevated the MCV. Reticulocytopenia was present in all patients, and reticulocytes were entirely absent in the majority. All patients had normal or elevated platelet counts; 16 patients had platelet counts greater than 400×10^9/L. Sixteen of the 26 patients had absolute neutrophil counts less than 1.5×10^9/L; 3 of these had counts of less than 1.0×10^9/L, but all had counts greater than 0.5×10^9/L. Seven of the 26 patients had direct and indirect

Accepted for publication December 13, 1988.

From The Children's Hospital (Dr Hays); and the Department of Pediatrics, University of Colorado School of Medicine, Denver (Drs Hays and Lane); and the Department of Pediatric Hematology/Oncology, Children's Hospital National Medical Center, Washington, DC (Dr Shafer).

Reprint requests to The Children's Hospital, 1056 E 19th Ave, Denver, CO 80218 (Dr Hays).

Coombs' tests performed at diagnosis; all were negative. Fifteen of 22 bone marrow aspirates showed erythroid hypoplasia with myeloid to erythroid ratios greater than 8:1. The bone marrows of the other seven patients showed erythroid maturation arrest.

Eighteen of these patients with TEC were treated with prednisone during the initial course of the illness. Two of the 26 required a transfusion of packed red blood cells prior to recovery. All of the patients demonstrated a marked reticulocyte response within 1 month and have maintained normal hemoglobin concentrations and reticulocyte counts since recovery. The seven patients with an erythroid maturation arrest in the marrow did not develop reticulocytosis quicker than patients with erythroid hypoplasia. All patients with neutropenia attained a normal neutrophil count within 1 to 2 weeks, in most cases prior to the reticulocyte response. To our knowledge, neutropenia has not recurred in any patient.

During the same period, of 288 children diagnosed with AL, 26 (9.5%) had normal platelet counts and white blood cell counts of less than 12×10^9/L, but all showed some clinical and hematological manifestations atypical for TEC. Fourteen (53%) of 26 patients presented with low-grade fever, bone pain was found in 14 patients (53%), and organomegaly was found in 8 patients (30%). Significant lymphadenopathy was found in 9 patients (Fig 3).[3] Ten of 26 patients had extreme leukopenia (white blood cell count, $<3.0 \times 10^9$/L) and significant neutropenia (absolute neutrophil counts $<0.5 \times 10^9$/L were found in 12 patients). In addition, 16 of 26 patients had circulating peripheral blast cells.

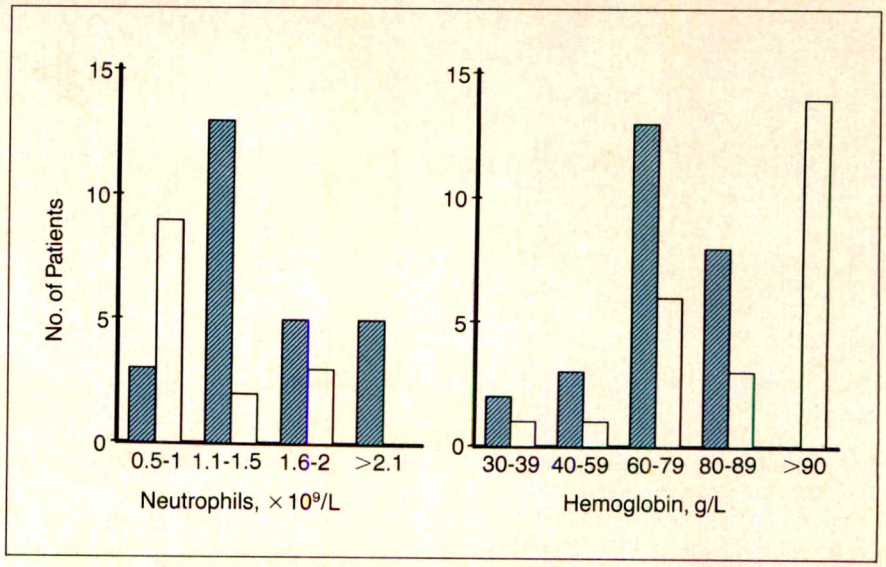


Fig 1.—Comparison of hematological data at diagnosis, transient erythroblastopenia of childhood vs acute leukemia. Shaded bars indicate patients with transient erythroblastopenia of childhood; open bars, patients with acute leukemia.

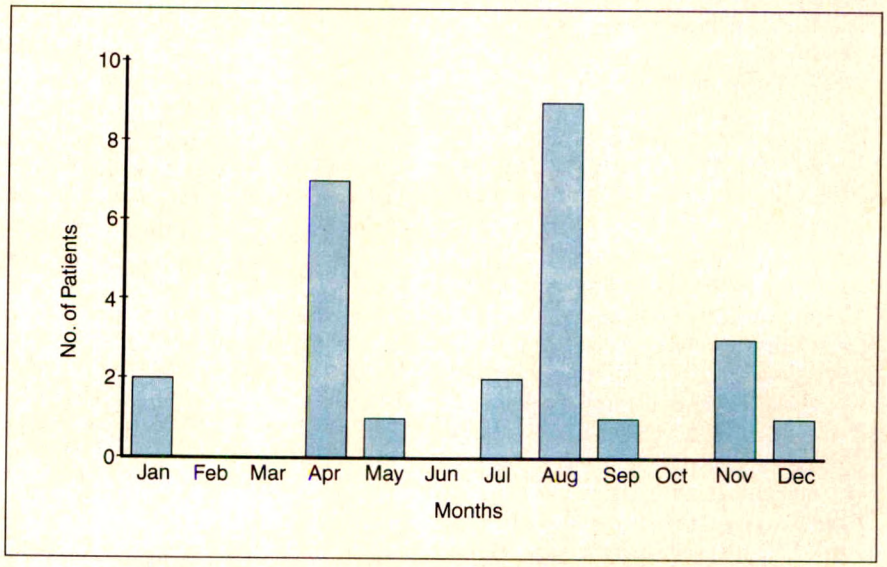


Fig 2.—Seasonal incidence of transient erythroblastopenia of childhood in 26 patients.

COMMENT

The 26 children with TEC shared many features with those previously described,[11] including a peak age incidence of between 6 months and 2 years, a consistent finding of normal to elevated platelets counts, and reticulocytopenia at the time of diagnosis without evidence of preexisting factors known to be associated with red blood cell aplasia. In addition, the frequency of preceding viral illness and the nonspecific findings on physical examination were also typical of the disorder.

Our data also confirm the recent observation[11] that some children with TEC present with neutropenia; 62% had absolute neutrophil counts less than 1.5×10^9/L at the time of diagnosis and 12% had less than 1.0×10^9/L. The bone marrow in the neutropenic patients did not show any quantitative, qualitative, or maturational abnormalities in myeloid series. Unfortunately, no other evaluation of the neutropenia was performed. In most neutropenic children, the absolute neutrophil count returned to normal prior to the appearance of reticulocytosis. In the four patients with neutropenia who did not receive steroid therapy, neutropenia recovered as rapidly as in the 12 children treated with steroids.

The majority of our patients with TEC presented during the spring and summer (Fig 2). Previous reports of TEC have suggested the seasonal clustering of cases.[6,9,11,14] Glader[11] noted that in three earlier reports [6,11,14] 67% of the cases occurred between June and Octo-

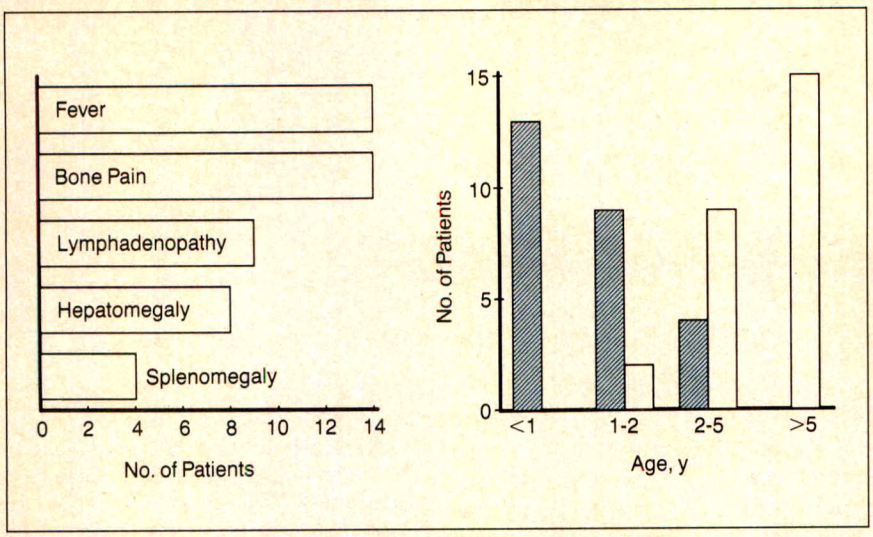


Fig 3.—Comparison of clinical data at diagnosis, transient erythroblastopenia of childhood vs acute leukemia. Right, Shaded bars indicate patients with transient erythroblastopenia of childhood; open bars, patients with acute leukemia.

ber. With the inclusion of our data and those recently published from Detroit,[9] only 57 (50%) of 114 cases have occurred during those 5 months of the year. Thus, while small clusters of cases may occur in a given location, no overall seasonal predominance is evident.

The clinical features at diagnosis of 288 children with AL were compared with those of TEC. Twenty-six patients (9.5%) with AL had a normal platelet count, but all showed some clinical manifestations atypical of TEC. These included fever, bone pain, lymphadenopathy, hepatosplenomegaly, extreme leukopenia or neutropenia, or the presence of blast cells on the peripheral blood smear. Thus, we did not uncover any cases of AL that were typical of TEC at the time the patient presented to our institution. The possibility that in some children AL might have mimicked TEC at any earlier time cannot be excluded. This might have occurred if children with an illness thought to be TEC were not referred to our hospital. However, the fact that this report comprises one of the largest series of TEC published to date argues against such a selection bias.

The bone marrow was examined in 22 of 26 patients with TEC, perhaps unnecessarily. Other causes of pure red blood cell aplasia, such as congenital hypoplastic anemia, are best distinguished from TEC by tests other than bone marrow aspiration.[10-12] Children with clinical features atypical of TEC are unlikely to have leukemia. Furthermore, since steroids are of no proved benefit in TEC, such children need not be partially treated in the unlikely event they subsequently prove to have leukemia. Finally, bone marrow examination was of no demonstrable prognostic value, as children with erythroid hypoplasia recovered as quickly as those with plentiful early erythroid precursors (erythroid maturation arrest). We conclude that many children with TEC do not require bone marrow aspiration for diagnosis or management.

We thank Shirley Uebelhoer for data collection and manuscript preparation.

References

1. Wranne L. Transient erythroblastopenia in infancy and childhood. *Scand J Haematol.* 1970;7:76-81.
2. Lovric VA. Anaemia and temporary erythroblastopaenia in children: a syndrome. *Aust N Z JMed.* 1970;19:34-39.
3. Toogood IRG, Speed IE, Cheney KC, Rice MS. Idiopathic transient normocytic, normochromic anaemia of childhood. *Aust Paediatr J.* 1978;14:28-33.
4. Wegelius R, Weber TH. Transient erythroblastopenia in childhood: a study of 15 cases. *Acta Paediatr Scand.* 1978;67:513-518.
5. Koenig HM, Lightsey AL, Nelson DP, Diamond KL. Immune suppression of erythropoiesis in transient erythroblastopenia of childhood. *Blood.* 1979;54:742-746.
6. Labotka RJ, Maurer HS, Honig GR. Transient erythroblastopenia of childhood: review of 17 cases, including a pair of identical twins. *AJDC.* 1981;135:937-940.
7. Dessypris EN, Krantz SB, Roloff JS, Lukens JN. Mode of action of the IgG inhibitor of erythropoiesis in transient erythroblastopenia of childhood. *Blood.* 1982;59:114-123.
8. Gerrits GPJM, van Oostrom CB, de Vaan GAM, Bakkeren JAJM. Transient erythroblastopenia of childhood: a review of 22 cases. *Eur J Pediatr.* 1984;142:266-270.
9. Bhambhami K, Inone S, Sarnaik SA. Seasonal clustering of transient erythroblastopenia of childhood. *AJDC.* 1988;142:175-177.
10. Wang WC, Mentzer WC. Differentiation of transient erythroblastopenia of childhood from congenital hypoplastic anemia. *J Pediatr.* 1976;88:784-789.
11. Glader BE. Diagnosis and management of red cell aplasia in children. *Hematol Oncol Clin North Am.* 1987;1:431-447.
12. Glader BE, Backer K, Diamond LK. Elevated erythrocyte adenosine deaminase activity in congenital hypoplastic anemia. *N Engl J Med.* 1983;309:1486-1490.
13. Dallman PR, Siimes MA. Percentile curves for hemoglobin and red cell volume in infancy and childhood. *J Pediatr.* 1979;94:26-31.
14. Kubic PT, Warkentin PI, Levitt CJ, Coccia PF. Transient erythroblastopenia of childhood (TEC) occurring in clusters. *Pediatr Res.* 1979;13:435. Abstract.

In Other AMA Journals

JAMA

Implications of Research and High Technology for Neonatal Intensive Care

M. Stahlman (*JAMA.* 1989;261:1791)

Abnormal Zinc Content in Human Milk

Risk for Development of Nutritional Zinc Deficiency in Infants

Stephanie A. Atkinson, PhD; Donald Whelan, MD, FRCPC; Robin K. Whyte, MB, FRCPC; Bo Lönnerdal, PhD

• An abnormally low concentration of zinc in mother's milk has been associated with clinical nutritional zinc deficiency in premature and term newborns. Defective mammary gland secretion of zinc was suggested as the causative factor. We investigated whether low milk zinc concentration might be reflected in an abnormality of the distribution of zinc between casein, whey, and fat components of the milk, in a reduction in the levels of milk citrate, a zinc-binding ligand, or in abnormal levels of copper and iron. Milk from mothers of four low-birth-weight infants was identified as being deficient in zinc content for the lactational stage. One infant had clinical signs of nutritional zinc deficiency. For two of the three infants with subclinical deficiencies in whom balance study data were available, the apparent zinc balance was negative (−5.7 and −6.0 μmol/kg per day). These milks were examined for content and distribution of zinc, copper, and iron, and citrate concentration. Although total zinc concentration (4.5 to 17.2 μmol/L) was below the 95% prediction interval (15.2 to 59.7 μmol/L) for the lactational stage, the distribution of zinc was normal between milk components. Levels of citrate (1.46 to 5.13 mmol/L) were also within normal limits, as were levels of copper (0.27 to 0.85 μmol/L and iron (0.41 to 1.13 μmol/L). We concluded that there was no indirect evidence of a secretory abnormality in milk zinc deficiency, but speculated that there might instead be an abnormality of zinc uptake by the mammary gland from the plasma.

(*AJDC*. 1989;143:608-611)

Accepted for publication October 12, 1988.

From the Department of Pediatrics, McMaster University, Hamilton, Canada (Drs Atkinson, Whelan, and Whyte); and the Department of Nutrition, University of California, Davis (Dr Lönnerdal). Dr Atkinson holds a Career Scientist Award from the Ministry of Health of Ontario, Canada.

Presented in part at the Sixth International Meeting on Trace Elements in Man and Animals, June 2, 1987, Asilomar, Calif.

Reprint requests to Department of Pediatrics, McMaster University, Hamilton, Ontario L8N 3Z5 Canada (Dr Atkinson).

Cases of nutritional zinc deficiency presenting as perioral and perineal acrodermatitis, delayed growth, irritability, and low blood zinc levels have been described during the first 2 to 6 months of life in both premature[1-5] and term[6-8] infants fed exclusively mother's milk. In all cases, the cause of the nutritional zinc deficiency in the infants was attributed to levels of zinc in the mother's milk that were far below the usual range of values reported for milk at similar lactational stages. However, there has only been speculation as to whether this was caused by defective mammary gland zinc secretion,[2,4] or whether it simply represented the lower end of a normal spectrum. We describe the quantitation of citrate, a zinc-complexing anion in human milk,[9] and the distribution of zinc, copper, and iron in casein, whey, and fat, and their concentration in "zinc-deficient" whole milk samples from four mothers. The clinical significance of exclusive feeding of an infant with zinc-deficient milk is demonstrated by a case report.

METHODS

Milk samples were obtained from mothers whose infants were patients at Chedoke-McMaster Hospitals, Hamilton, Canada. We were alerted to assess, retrospectively, the possibility of low zinc concentrations in milk samples obtained for the purpose of nutrition research studies, after an infant (case 1) presented with fulminant clinical zinc deficiency after 4.5 months of exclusive breast-feeding.

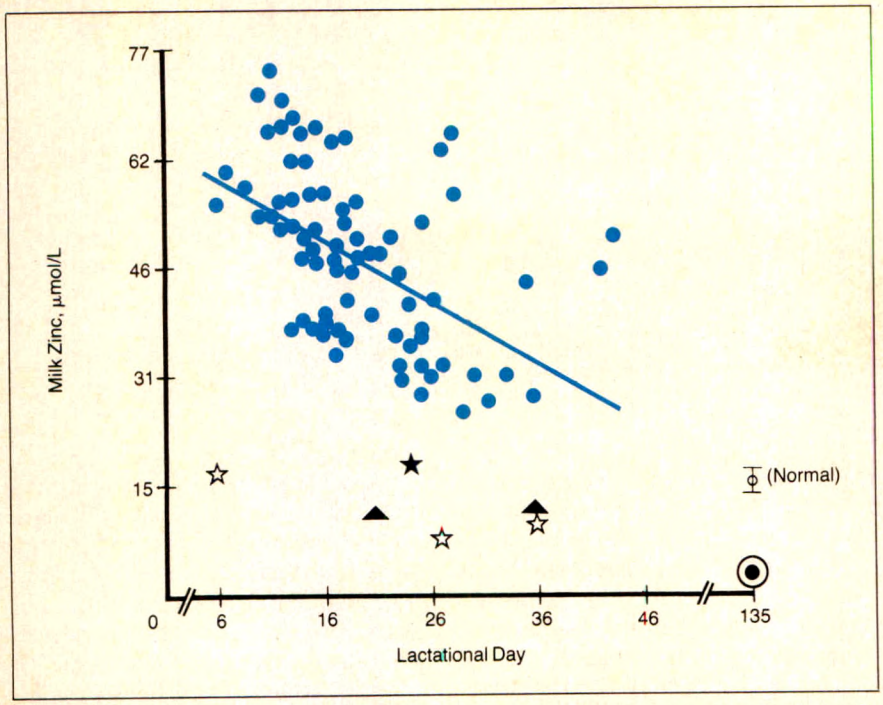
Milk samples were obtained by complete emptying of the breast using acid-washed electric or manual breast pumps. An aliquot of milk was separated by ultracentrifugation at 189 000*g* for 1 hour and analyzed in duplicate for zinc, copper, and iron in the whole milk, milk fat, pellet (casein), and whey fractions by atomic absorption spectrophotometry following wet ashing.[10] In case 2, there was a premature infant for whom we conducted a metabolic balance study as part of the clinical investigation of the diagnosis of acrodermatitis enteropathica, which had been documented in a previously born sibling. Cases 3 and 4 were part of a nutritional study conducted by two of us (S.A.A. and R.K.W.),[11] for which a 72-hour metabolic balance for zinc was performed according to previously published methods.[12]

RESULTS

Case Presentation

A male infant (case 1) was referred to Chedoke-McMaster Hospitals at a postnatal age of 4.5 months by the family physician because of a dermatitis. He had been born after a 33-week gestation at a birth weight of 1760 g. With the exception of the occasional feeding of formula in the hospital when breast milk was unavailable, this infant was fed exclusively his mother's milk, either expressed or suckled. No mineral supplements had been prescribed at any time.

A rash was first noted as small red spots on the thighs, buttocks, and face at 3 months of age. As the rash worsened, it was treated by the family physician with several antibacterial agents, both topical (clotrimazole, bacitracin) and oral (cloxacillin sodium, cefaclor), but without response. The rash began to peel with bleeding and then appeared on the eyelids, feet, and fingers. Hexachlorophene cream and 1% hydrocortisone were administered without effect. At 3.5 months of age, the infant was circumcised, and healing was incomplete a month later. He displayed occasional irritability but otherwise nursed reasonably well until 2 weeks before admission, when his mother noted a decrease in appetite and weight gain. On admission, his weight was 4.1 kg (5th to 10th percentile for a corrected age of 2.5 months), length was 37 cm (25th to 50th



Zinc content of milk in relation to lactational day indicates regression line for normal preterm milk ($y = 4.22 - 0.056x$, $r = -.54$, $P < .01$).[11] Zinc-deficient milks are indicated by closed circle within open circle (case 1), closed star (case 2), open star (case 3), and triangle (case 4). Normal indicates normal reference value for zinc content of term mothers at 4 to 6 months of lactation.[18]

Table 1.—Distribution of Zinc and Citrate Content of Milk Samples

Case	Lactation, d	Zinc, μmol/L Fat	Whey	Casein	Total	Predicted Normal Total	Citrate,* mmol/L
1	135	1.8	2.2	0.6	4.5	15.2†	1.85
2	25	3.2	14.1	1.2	7.5	44.3‡	1.74
3	6	7.4	15.2	0.6	17.2	59.7‡	2.50
	27	10.8	6.6	0.6	7.8	41.7‡	1.46
	36	4.6	3.5	0.9	9.1	33.8‡	1.44
4	21	3.1	6.5	0.1	11.1	46.7‡	5.13
	35	5.7	4.6	1.4	11.7	34.8‡	5.07

*Normal citrate concentration of human milk is 1 to 2 mmol/L.[9]
†Normal value in the literature at 4 to 6 months of lactation.[17]
‡Lactational stage adjusted value as calculated from linear regression analysis for preterm milk zinc (see Figure; $y = 4.22 - 0.056x$, $r = -.54$, $P < .01$[11]).

percentile), and head circumference was 40 cm (75th percentile).[13]

By the time of his admission to the hospital (at 4.5 months of age), the inflammation was distributed over the cheeks, chin, nasolabial folds and pinnae, the dorsa of the fingers, and both big toes. In the perineal area, there were punctate erosions and a diffuse erythema that was symmetrical and well demarcated with an erythematous border. There were a few satellite lesions but no scales. The center blanched to pressure. The pattern of the rash was similar to that classically associated with familial acrodermatitis enteropathica.[14] Pertinent biochemical investigations on admission and our laboratory normal values for infants were as follows: serum zinc, 9.6 μmol/L (normal, 11.5 to 18.5 μmol/L); hemoglobin, 96 g/L (normal, 95 to 118 g/L[15]); alkaline phosphatase, 241 U/L (normal, 30 to 120 U/L); and phosphorus, 0.98 mmol/L (normal, 1.8 to 2.1 mmol/L).[16] His mother had normal serum zinc (14.0 μmol/L) but low milk zinc levels (Table 1, case 1). Oral supplements of zinc sulfate providing 1 mg of elemental zinc per kilogram of body weight per day were prescribed. After 1 week of therapy, his dermatitis had cleared on his face and fingers and only minor remnants of the marginating rash in his buttock area remained. Because of a low hemoglobin level, an iron supplement was prescribed providing 2 mg of elemental iron per kilogram per day. A bone density measurement of the one third distal radius done at this time measured 77 mg/cm. The normal range for infants of this corrected postnatal age is 75 to 100 mg/cm.[17]

At a follow-up visit, 6 weeks after the initiation of zinc therapy, his skin was clear. He had been breast-fed, with only zinc and iron supplements and about 8.3 g of rice cereal with 2% cow's milk daily. Most blood biochemistry had returned to the normal range: zinc, 18 μmol/L; phosphorus, 1.69 mmol/L; and hemoglobin, 100 g/L. The exception was the alkaline phosphatase level, which had risen to 807 U/L following zinc supplementation. Bone mineral density had also increased to 92 mg/cm, which is within the cited normal range.[17]

Trace Element Composition of Milks

The analysis of zinc was completed in six milk samples from three mothers whose infants were involved in metabolic balance studies conducted by two of us (S.A.A. and R.K.W.). All were premature infants: in case 2, the gestational age was 30 weeks and the birth weight was 1470 g; case 3, age was 28 weeks and weight 1430 g; case 4, age was 28 weeks and weight 1120 g for one twin and 1090 g for the other twin. The concentration of zinc in milk from cases 1 to 4 was compared with values for preterm milk over the first 46 days of lactation as previously described by our laboratory.[11] Milk zinc concentration declined with progressing lactation (Figure). Prediction intervals for milk zinc at each lactational day were derived by linear regression. Any observed value that was below the lower 95% prediction limit for a specific lactational day was judged to be zinc-deficient. Cases 2, 3,

and 4 met this criterion. The zinc content of milk from the mother in case 1 was one third the value reported for milk at 4 to 6 months of lactation (15 ± 0.8 μmol/L).[18] Milk zinc content was not significantly correlated with expressed milk volume (range, 790 to 1100 mL/d) ($y = 526 - 0.37x$, $r = -.408$, $n = 8$, not significant); thus, lactational capacity was not considered a significant variable.

Zinc content of the fat, whey, casein, and whole milk fractions are presented in Table 1. Zinc was found principally in the whey (41% to 88%) and fat (14% to 50%) fractions of the milk. The concentration of the zinc-binding ligand, citrate, was within the previously reported range for human milk except for case 4, in which it was higher (Table 1). The content of copper in the milk samples varied with the lactational stage, ranging from 0.85 to 0.27 μmol/L, which was similar to values reported for milk from mothers of term infants during early lactation.[10] The distribution of copper between the fat ($29.3\% \pm 2.7\%$), whey ($52.2\% \pm 3.9\%$), and casein ($9.6\% \pm 1.7\%$) fractions was also similar to that of the previous report.[10] The iron content of the milks ranged from 1.13 to 0.41 μmol/L, within the range of previously published values.[10] The greatest proportion of iron was in the whey fraction ($53.5\% \pm 6.9\%$), with approximately equal amounts in the fat ($23.8\% \pm 1.9\%$) and casein ($20.8\% \pm 3.2\%$) fractions.

For two infants (cases 2 and 3), milk, urine, and stool samples were available from 72-hour metabolic studies so that apparent zinc balances were calculated (Table 2). The normal reference data are derived from the studies published by us on low-birth-weight infants fed their mothers' milk in the first 2 months of life.[11]

Table 2.—Zinc Balance in Infants Fed Zinc-Deficient Milk

	Infant Age at Study, d	Zinc, μmol/kg per Day			
		Intake	Fecal Excretion	Urinary Excretion	Apparent Retention
Case 2	26	3.0	5.3	3.4	−5.7
Reference values	35 ± 4	54.5 ± 0.5	8.5 ± 1.2	1.8 ± 0.3	−4.9 ± 1.3
Case 3	16	2.9	6.6	2.3	−6.0
Reference values	20 ± 1	7.7 ± 0.5	7.9 ± 0.8	2.1 ± 0.3	−2.7 ± 0.9

*Values given are for the reference population[11] at a similar gestational and postnatal age as the cases presented and are the mean ± SD.

COMMENT

In case 1, in which the infant was solely breast-fed, the clinical and biochemical manifestations at presentation and the rapid response to oral zinc therapy were characteristic of neonatal nutritional zinc deficiency.[1-8] Reported clinical response to zinc therapy has been consistently dramatic and complete, even though the oral dose of elemental zinc prescribed ranged from 11 mg/kg per day[6] to 1.0 mg/kg per day (case 1). Since the infant responded clinically to zinc supplementation as quickly as in previously described cases,[1-8] it appears that zinc therapy in excess of 1 mg/kg of body weight is not necessary to obtain the desired response.

Most reports of cases similar to the one we described are of infants born prematurely (27 to 33 weeks of gestation)[1-5] who were diagnosed with the zinc deficiency at 2 months of age or older. This coincides with the "catch-up" growth phase during which zinc demands for growth and metabolic function are not met by exclusive breast-feeding with a milk that contains only about one third the expected concentration of zinc. But the opportunity to have carried out zinc balance studies in two of the cases described demonstrated that a large net negative deficit of zinc could accrue during early neonatal life. Zinc retention in premature infants fed mother's milk and studied at a postconceptual age of less than 38 weeks have been reported by us[11] (Table 2) and others[19-21] to be negative, possibly due to an immaturity in gastrointestinal transport/secretion of zinc in prematurely born infants.[19] In cases 2 and 3, low milk zinc concentrations resulted in even larger negative balances in the first 4 weeks of life (Table 2).

Suckling pups of mice homozygous for the lethal milk gene (lm/lm) developed signs of zinc deficiency by 8 days of age.[22] The clinical signs of the lethal milk mutation were similar to those seen in case 1 and reported by others.[1-8]

Two important observations made in case 1 not commented on in previous reports were the rise in serum alkaline phosphatase and phosphorus levels and the increase in bone mineral density in association with zinc therapy. Zinc is a major component of bone, with 40% of body zinc thought to be present in the skeleton.[23] Animal studies of zinc deficiency suggested that zinc may regulate osteoblasts and osteoclast proliferation.[24,25] Zinc supplementation in animals resulted in an increase in diaphyseal alkaline phosphatase activity, suggesting that the zinc stimulated osteoblast proliferation.[26] In rapidly growing premature infants, elevations in alkaline phosphatase levels have been observed especially in those infants exclusively fed mother's milk.[12,27] Correction of zinc deficiency in the infant in case 1 would have allowed for normal bone turnover to proceed and alkaline phosphatase level to increase. Normalization of plasma phosphorus level would also promote bone mineralization.

It is difficult to explain the positive response in plasma phosphorus level on a metabolic basis. However, a small increase in phosphorus intake from infant cereal (8.3 g/d) with 2% cow's milk (75 mL/d) may have contributed sufficient dietary phosphorus (approximately 2.6 mmol of phosphorus per day) to correct the relative phosphorus-deficient state known to occur in breast-fed premature infants.[12,27]

In earlier case reports of zinc deficiency in infants associated with low zinc content of mother's milk,[1-8] the distribution of zinc and other trace elements in these milks and the concentration of known metal complexing proteins were not reported. Despite the low levels of milk zinc, milk iron and copper concentrations were normal, and trace elements were normally distributed

among the milk fractions. Additionally, there was no discernible abnormality in zinc distribution between the lipid and the two major protein fractions (casein and whey) of the milk. One other possible zinc ligand that was not investigated is free amino acids. But since zinc bound to amino acids is proportionately a very small fraction of total zinc, at least in serum and presumably also in milk, it is not likely that this fraction is responsible for the lower milk zinc concentration observed. Maternal deficiency in circulating zinc could be a potential reason for limited mammary uptake of zinc, but in the mother of our case 1, as well as in previous reports,[2,4] this theory has not been supported. Maternal zinc supplements elevated maternal serum zinc levels but not the milk zinc level.[3,4] In early lactation (2 to 3 weeks), zinc was higher in milk (28 to 62 μmol/L) relative to plasma.[28] Zinc is actively transported into the mammary gland, possibly with a low-molecular-weight complexing anion such as citrate.[9] Contrary to previous speculation,[2,4] a defective mammary secretory mechanism for zinc into milk was likely not the cause of low milk zinc content since citrate levels in all milk samples were normal. It appears more likely that mechanisms that accrue zinc from the circulation (plasma) into the mammary gland may be abnormal. A systemic low uptake of zinc into the gland but with normal synthetic and secretory mechanisms would explain a low concentration but normal distribution of zinc in the milk. The reasons for poor mammary zinc uptake may represent an inherited disorder, but further investigation is needed.

Our identification of four cases of zinc-deficient milk in the local infant population in a 2-year period suggests that this milk abnormality may not be rare but perhaps is not always diagnosed because it exists in early infant life as a subclinical biochemical deficiency. A slowing of the growth rate with persistent perioral or perianal rash with or without diarrhea in infants fed solely breast milk may be consistent with zinc depletion. Low-birth-weight infants appear to be particularly at risk. As a result, an evaluation of milk zinc content should be considered.

This work was financially supported by the Medical Research Council of Canada, Ottawa, and the National Institutes of Health, Bethesda, Md.

We gratefully acknowledge the technical assistance of Carol Glazier, MS, and Debra Fraser.

References

1. Aggett PJ, Atherton DJ, More J, et al. Symptomatic zinc deficiency in a breast-fed preterm infant. *Arch Dis Child*. 1980;55:547-550.
2. Weymouth RD, Czarnecki D. Symptomatic zinc deficiency in premature, breast-fed infants associated with defective mammary gland zinc secretion. *Aust Paediatr J*. 1981;17:131.
3. Parker PH, Helinek GL, Meneely RL, Stroop S, Ghishan FK, Greene HL. Zinc deficiency in a premature infant fed exclusively human milk. *AJDC*. 1982;136:77-78.
4. Zimmerman AW, Hambidge KM, Lepow ML, Greenberg RD, Stover ML, Casey CE. Acrodermatitis in breast-fed premature infants: evidence for a defect of mammary zinc secretion. *Pediatrics*. 1982;69:176-183.
5. Murphy JF, Gray OP, Rendall JR, Hann S. Zinc deficiency: a problem with preterm breast milk. *Early Hum Dev*. 1985;10:303-307.
6. Blom I, Jameson S, Krook F, et al. Zinc deficiency with transitory acrodermatitis enteropathica in a boy of low birth weight. *Br J Dermatol*. 1980;104:459-464.
7. Bye AME. Transient zinc deficiency in a full-term breast-fed infant of normal birth weight. *Pediatr Dermatol*. 1985;2:308-311.
8. Kuramoto Y, Igarashi Y, Kato S, Tagami H. Acquired zinc deficiency in two breast-fed mature infants. *Acta Derm Venereol (Stockh)*. 1986;66:359-361.
9. Lonnerdal B, Stanislowski AG, Hurley LS. Isolation of a low molecular weight zinc binding ligand in human milk. *J Inorg Biochem*. 1980;12:71-78.
10. Fransson GB, Lonnerdal B. Effect of freezing on distribution of trace elements and minerals in human and cows' milk. *Nutr Res*. 1983;3:845-853.
11. Atkinson SA, Fraser D, Stanhope R, Whyte R. Zinc balance in premature infants fed their mothers' milk: effect of postnatal age. In: Hurley LS, Lonnerdal B, Keen CL, Rucker RB, eds. *Trace Element Metabolism in Man and Animals*. 6th ed. New York, NY: Plenum Publishing Corp. In press.
12. Atkinson SA, Radde IC, Anderson GH. Macromineral balances in premature infants fed their own mothers' milk or formula. *J Pediatr*. 1983;102:99-106.
13. Tanner JM, Whitehouse RH. Clinical and longitudinal standards for height, weight, height velocity, weight velocity and stages of puberty. *Arch Dis Child*. 1976;51:170-179.
14. Moynahan EJ, Barnes PM. Zinc deficiency and a synthetic diet for lactose intolerance. *Lancet*. 1973;1:676-677.
15. Black PJ, Barfan P. The blood and bone marrow during growth and development. In: Paris JA, Dobbing J, eds. *Scientific Foundations of Pediatrics*. London, England: Heinemann Medical Books Ltd; 1981.
16. Harrison HH, Harrison HC. *Disorders of Calcium and Phosphate Metabolism in Childhood and Adolescence*. Philadelphia, Pa: WB Saunders Co; 1979:104.
17. Greer FR, Lane J, Weiner S, Mazess RB. An accurate and reproducible absorptiometric technique for determining bone mineral content in newborn infants. *Pediatr Res*. 1983;17:259-262.
18. Dewey KG, Finley DA, Lonnerdal B. Breast milk volume and composition during late lactation (7-20 months). *J Pediatr Gastroenterol Nutr*. 1984;3:713-720.
19. Dauncey MJ, Shaw JCL, Urman J. The absorption and retention of magnesium, zinc and copper by low birthweight infants fed pasteurized human breast milk. *Pediatr Res*. 1977;11:1033-1039.
20. Voyer M, Davakis M, Antener I, Valleur D. Zinc balances in preterm infants. *Biol Neonate*. 1982;42:87-92.
21. Casey CE, Hambidge KM. Trace minerals. In: Tsang RC, ed. *Vitamin and Mineral Requirements in Preterm Infants*. New York, NY: Marcel Dekker Inc; 1985:153-184.
22. Piletz JE, Ganschow RE. Lethal milk mutation results in dietary zinc deficiency in nursing mice. *Am J Clin Nutr*. 1979;31:560-562.
23. Shaw JCL. Trace elements in the fetus and young infant, I: zinc. *AJDC*. 1979;133:1260-1268.
24. Pleban PA, Numerof BS, Wirth FH. Trace element metabolism in the fetus and neonate. *Clin Endocrinol Metab*. 1985;14:545-566.
25. Leek JC, Keen CL, Vogler JB, et al. Long-term marginal zinc deprivation in rhesus monkeys, IV: effects on skeletal growth and mineralization. *Am J Clin Nutr*. 1988;47:889-895.
26. Yamaguchi M, Yamaguchi R. Action of zinc on bone metabolism in rats: increases in alkaline phosphatase activity and DNA content. *Biochem Pharmacol*. 1986;35:773-777.
27. Sagy M, Birenbaum E, Balin A, Orda S, Barzilay Z, Brish M. Phosphate-depletion syndrome in a premature infant fed human milk. *J Pediatr*. 1980;96:683-685.
28. Moore MEC, Moran JR, Greene HL. Zinc supplementation in lactating women: evidence for mammary control of zinc secretion. *J Pediatr*. 1986;105:600-602.

In Other AMA Journals

JAMA

The Natural History of Prenatally Diagnosed Cerebral Ventriculomegaly

A. Drugan; B. Krause; A. Canady; I. E. Zador; A. J. Sacks; M. I. Evans (*JAMA*. 1989;261:1785-1787)

Pediatric Patients, Race, and DRG Prospective Hospital Payment

Eric Munoz, MD, MBA; Eugenio Barrios, MS; Houston Johnson, MD; Jonathan Goldstein, MPA; Katherine Mulloy, AS; Donald Chalfin, MD; Leslie Wise, MD

• The diagnosis related group (DRG) prospective hospital payment system contains inequities in hospital payment for certain groups of patients. Patients of lower socioeconomic status may be underreimbursed by DRGs. We analyzed pediatric patients and hospital resource consumption by race (white, Hispanic, and black) using a DRG prospective payment "all payer" system. All hospitalized pediatric admissions over a 3-year period (N = 14 489) were analyzed by race at a large academic medical center. Mean hospital length of stay and cost per patient (adjusted for DRG weight index) was significantly greater for black and Hispanic pediatric patients compared with whites. Financial risk as measured by outliers and losses under DRGs was greater for blacks and Hispanics compared with whites. Black and Hispanic patients had a higher proportion of emergency admission to the hospital compared with whites, a greater severity of illness (as measured by total *International Classification of Diseases, ninth revision, Clinical Modification* codes), and (on average) higher diagnostic costs for each episode of illness. Our data suggest that black and Hispanic pediatric patients have a greater hospital resource consumption (adjusted for DRG group case mix) compared with whites, at least at our large medical center in the Northeast. Hospitals that treat greater numbers of black and Hispanic pediatric patients may be at a substantial disadvantage under per-case DRG payment.

(*AJDC*. 1989;143:612-616)

Accepted for publication December 22, 1988.

From the Departments of Surgery (Drs Munoz, Johnson, and Wise, Messrs Barrios and Goldstein, and Ms Mulloy) and Medicine (Dr Chalfin), Long Island Jewish Medical Center, New Hyde Park, NY; and the Hostos Community College of the City University of New York, Bronx (Mr Barrios). Dr Munoz is now with the University of Medicine and Dentistry of New Jersey, University Hospital, Newark.

Reprint requests to Department of Surgery, Long Island Jewish Medical Center, New Hyde Park, NY 11042 (Dr Munoz).

There are a number of health policy questions facing the nation regarding hospital payment, in particular how to improve the equity of the diagnosis related group (DRG) prospective hospital payment system.[1] Hospitals are stratified in the DRG classification system by criteria such as urban or rural location, teaching or nonteaching, and disproportionate share vs nondisproportionate share (ie, those hospitals treating poor patients).[2] A number of states have become DRG "all payer" and use the Medicare DRG model, whereby Medicare, Medicaid, Blue Cross, and commercial insurance pay for hospitalized patients using the DRG method.[3] All-payer systems were constructed to retard cost shifting between payers. The rise in Medicare Part A hospital expenditures has slowed during the past 5 years.[4] The hospital industry has alleged, meanwhile, that profit margins have dropped because of the federal Medicare DRG system, and that an increasing number of hospitals are in a precarious situation.[5]

An important health policy question facing the nation is the degree of equity that can be achieved in a crude "product"-grouping scheme such as the DRG. The DRG classification system (for example) explains only about 40% of cost variance for each patient, ie, it predicts only a modest degree of resource use. Analyses have shown that certain types of patients may cause financial problems to institutions under DRG payment. Thus, patients admitted in an emergency, those transferred from other institutions, and those with a higher number of comorbidities or a greater severity of illness appear to be underreimbursed by the DRG hospital payment system.[6-9] Strategic planners hope that profits under DRG payment generated by some patients will be used at the institutional level to subsidize other financially risky patients. Many in the health sector are skeptical of this happening; the factors affecting this subsidization are related to a variety of forces.

Analysis of the federal DRG system regarding patients of lower socioeconomic status at one large Boston, Mass, teaching hospital suggested that poorer patients may be underreimbursed by DRGs.[10] Studies of DRG financial risk for patients by route of admission (ie, emergency vs nonemergency) into the hospital have shown that emergency admissions per DRG are generally more expensive compared with nonemergency admissions, and usually incur financial loss.[11] Minority patients are more likely (on average) to be admitted emergently to the hospital, and thus even insured minority patients may be a financially unattractive population under DRGs.[12] The current DRG hospital reimbursement methodology may offer certain financial disincentives to treat minority Americans (particularly black and Hispanic patients).

The present study analyzed resource consumption for hospitalized minority pediatric patients treated at a large northeastern medical center using the DRG format by race, ie, white, black, and Hispanic.

SUBJECTS AND METHODS

The Long Island Jewish Medical Center (LIJMC) is an 805-bed academic medical center located in suburban New York, NY, with a 155-bed children's hospital. It has active teaching programs in all specialties, has a payer mix similar to other "voluntary" not-for-profit hospitals (ie, of admissions, 21.6% are covered by Medicare, 6.2% are covered by Medicaid, 47.0% are covered by Blue Cross, 18.4% are covered by commercial insurance, and 6.8% are nonpaying or self-paying). The LIJMC has 23 673 admissions annu-

ally and 55 000 emergency department visits. We analyzed all pediatric admissions (N = 14 489) during a 3-year period (ie, 1985 to 1987) to the medical center. The LIJMC came under the fully implemented Medicare DRG reimbursement system as of January 1, 1987, and it came under a New York State DRG "all payer system" as of January 1, 1988. The hospital is a voluntary not-for-profit hospital at the border of New York City and Long Island. It serves a middle class section of New York City–Long Island, as well as working-class sections. There are no significant distorted flows of patients related to socioeconomic status, race, or clinical services.

A number of characteristics were analyzed by race for white, black, and Hispanic pediatric patients. Race is assigned by an admitting clerk on admission to the hospital as white, black, Hispanic, Oriental, or other. Analyzed for each pediatric patient by race were mean age, hospital length of stay, and total hospital cost, the number of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis codes, the number of *ICD-9-CM* procedure codes, and the total number of *ICD-9-CM* diagnosis and procedure codes (as a proxy for severity of illness). Profit or loss under DRG all payer reimbursement was assessed, as were the number and percentage of outliers for each group. Diagnostic costs (computed as the total of laboratory costs and diagnostic radiology costs) were measured for all pediatric patients. Adjustment by DRG weight index (to standardize hospital resource consumption per unit of DRG) for hospital length of stay, total hospital cost, and diagnostic costs for each patient by race was performed using the Medicare DRG weight index for that particular DRG. Route of admission (ie, emergency department vs other department) was analyzed for white, black, and Hispanic pediatric patients. Statistical analysis was performed between groups of patients using Student's *t* test and/or an ANOVA.

New York State Simulated All Payer Methodology

We simulated a DRG all payer system in constant dollars by using the federal Medicare DRG payment methodology (in effect during the study period in New York) in New York for Medicare, and the New York State all payer DRG methodology for Medicaid, Blue Cross, and other commercial insurance. This was the current New York State all payer system in effect for our hospital as of January 1, 1988. Diagnosis related group payments by non-Medicare payers were *deflated* by the hospital market basket adjustment (4.1% for 1985, 3.1% for 1986, and 3.5% for 1987) for a simulated "real" DRG reimbursement for fiscal years 1985, 1986, and 1987. Thus, we used our clinical financial data base to simulate a typical DRG all payer system (New York State became all payer on January 1, 1988) in constant dollars for one large academic medical center, and adjusted DRG payment by a standard amount to a base year. The federal and state DRG methodology for both inlier and outlier payment (both cost and length of stay) was used; DRG weight indexes were those federal rates in effect during the study period for Medicare, or those New York State rates for other payers. The LIJMC is categorized as an urban teaching hospital by the DRG reimbursement scheme.

LIJMC Hospital Costing Methodology

Hospital cost per pediatric patient was obtained by using per-patient charge-specific data and converting these charges to hospital costs. Cost-to-charge ratios used by our hospital accounting division were used to convert charges to costs. The following ratios were used for each hospital service category:

Category	Ratio
Room and board	0.75
Laboratory	0.40
Blood (storage, processing, transfusion, and products)	1.15
Surgical pathology	2.42
Diagnostic radiology	0.94
Therapeutic radiology	1.71
Operating room	1.10
Recovery room	1.15
Respiratory therapy	0.76
Electrocardiology	0.25
Electroencephalography	1.40
Medical supplies	1.00
Pharmacy	1.00
Diagnostic ultrasound	0.46
Computed tomographic scan	0.53
Emergency department	0.91
Pulmonary function	0.08

Thus, to obtain hospital costs for charges of $100 the following calculations were performed: blood, $100 × 1.15 = $115; respiratory therapy, $100 × 0.76 = $76; and pharmacy, $100 × 1.00 = $100. Although cost-to-charge ratios may only give general information regarding each patient's true costs, this was the most accurate costing method in use at our hospital during the study period. Hospital length of stay and hospital charges could also be used as a proxy for "expense."

RESULTS

Total costs for the 14 489 pediatric patients for the 3-year study period were $84 085 057. The emergency admission rate for all pediatrics patients was 30.9%; black (6.48 years) and Hispanic (6.28 years) pediatric patients were older than white (5.87 years) patients (Table 1). There was a significant difference in mean DRG weight index per patient between blacks, Hispanics, and whites. Mean hospital length of stay per patient was highest for Hispanics (9.07 days) and lowest for whites (6.15 days). Mean total hospital cost per patient was highest for Hispanics ($8067), followed by blacks ($7076) and then whites ($5357). The mean total number of *ICD-9-CM* diagnostic and procedure codes was highest for Hispanics and lowest for whites (Table 1).

The mean hospital length of stay per pediatric patient (adjusted for DRG weight index) was higher for blacks (10.18 days) ($P<.0001$) and Hispanics (9.55 days) ($P<.002$) compared with whites (7.75 days) (Table 2). The mean hospital cost per patient (adjusted for DRG weight index) was significantly higher for blacks ($8408) ($P<.0001$) and Hispanics ($8099) ($P<.002$) compared with whites ($6744) (Fig 1). Blacks (5.13 codes per patient) ($P<.0003$) and Hispanics (5.22 codes per patient) ($P<.02$) also had a significantly greater number of total *ICD-9-CM* codes per patient (as a proxy for severity of illness), adjusted for DRG weight index, compared with whites (4.83 codes per patient) (Table 2). Blacks ($P<.0001$) and Hispanics ($P<.0005$) had a significantly greater loss per patient under DRG all payer reimbursement compared with whites; all patients, however, generated losses under DRGs. The percentage of outliers were highest for blacks (6.27%), followed by Hispanics (5.79%), and then whites (3.86%) (Fig 2). The rate of admissions through the emergency department was highest for blacks (36.3%) ($P<.0001$), followed by Hispanics (30.0%), and then whites (29.6%) (Table 2). Diagnostic costs (measured by laboratory and diagnostic radiology charges) were highest (after adjustment for DRG weight index) for blacks at $768 per patient ($P<.0001$) and Hispanics at $726 per patient ($P<.01$), compared with whites at $608 per patient (Fig 3).

COMMENT

The United States is involved in a struggle to provide "comprehensive cost-effective" medical services to its citizens, but must do so at an acceptable cost to our society. The latest in major hospital payer trends in the post–World War II era is a "per-case" hospital pay-

Table 1.—Race and Hospital Resource Characteristics for Pediatric Patients*

Race	Age, y (*P*)	DRG Weight Index (*P*)	Hospital Length of Stay, d (*P*)	Total Hospital Cost, $ (*P*)	Total ICD-9-CM Codes (*P*)
Black (n=2757)	6.48±5.82 (.003)	1.0385±1.0187	8.33±20.74 (.0001)	7076±16 780 (.0001)	3.33±2.55 (.0001)
Hispanic (n=639)	6.28±6.04 (.02)	1.2035±1.1389 (.0001)	9.07±26.55 (.0001)	8067±23 478 (.0001)	3.77±2.84 (.0001)
White (n=11 093)	6.87±6.01	1.0112±0.8643	6.15±14.98	5357±12 253	3.03±2.14

*Values are the mean±SD per patient. DRG indicates diagnosis related group; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification. *P* values indicate a statistically significant difference from white patients. Black and Hispanics were statistically different from each other for total ICD-9-CM codes ($P<.0001$) and DRG weight index ($P<.003$).

Table 2.—Resource Characteristics by Race Adjusted for Case Mix, Profit/Loss, and Emergency Admission for Pediatric Patients*

Race	Length of Stay/Weight Index (*P*)†	*ICD-9-CM*/Weight Index (*P*)†	Loss, $ (*P*)‡	Mean (±SD) Rate of Emergency Admission, % (*P*)§
Black	10.18±22.73 (.0001)	5.13±4.03 (.0003)	3030±14 410 (.0001)	36.3±48.1 (.0001)
Hispanic	9.55±21.90 (.002)	5.22±4.48 (.02)	3257±21 000 (.0005)	30.0±45.9
White	7.75±13.31	4.83±3.78	1614±10 754	29.6±45.7

**ICD-9-CM* indicates *International Classification of Diseases, Ninth Revision, Clinical Modification*. *P* values indicate a statistically significant difference from white patients.

†Mean (±SD) per-patient length of stay or total *ICD-9-CM* codes divided by each patient's diagnosis related group weight index (note that the value is not the simple average of length of stay or *ICD-9-CM* codes divided by weight index because of statistical distributions).

‡Mean (±SD) or loss under simulated New York State "all-payer" diagnosis related group payment.

§Blacks and Hispanics were statistically different from each other for rate of emergency admission ($P<.003$).

ment method using DRGs, which introduces economic risk and uncertainty into hospital payment. When the federal DRG system was implemented, its founders included additional payment for the costs of the care for "poor" patients (called *disproportionate share payment*). Only hospitals taking care of great numbers of poor patients receive this disproportionate share adjustment, however. Using a typical DRG all payer hospital reimbursement system, we analyzed hospital resource consumption for pediatric patients by race. Black and Hispanic pediatric patients had (on average) a greater hospital length of stay and total hospital cost per patient compared with whites. Black and Hispanic pediatric patients also had more severe illness and had more financial risk under DRG prospective hospital payment compared with white patients' financial risk under DRG prospective hospital payment. Black and Hispanic pediatric patients had a greater percentage of emergency admissions and higher diagnostic costs compared with white pediatric patients. These findings have implications for DRG prospective hospital payment policy for pediatric patients.

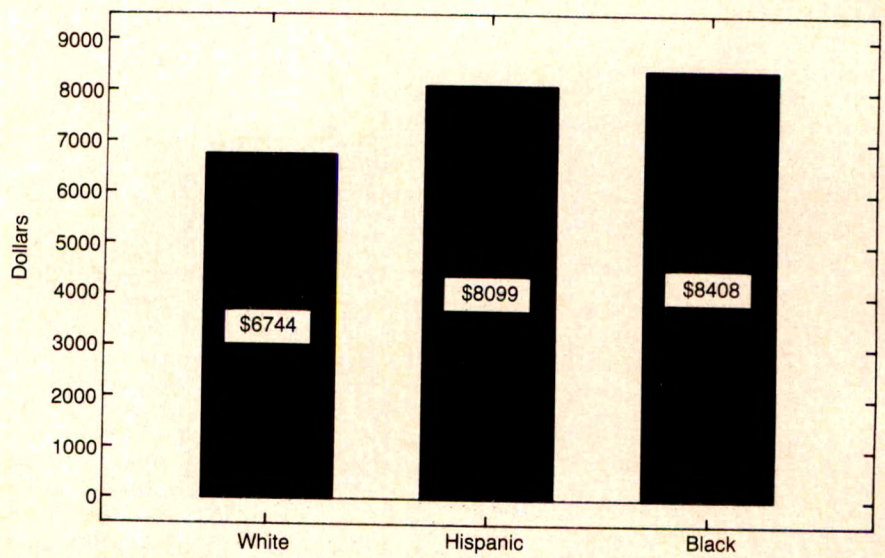


Fig 1.—Black ($P<.0001$) and Hispanic ($P<.001$) pediatric patients had a significantly higher mean total hospital cost per patient (adjusted for diagnosis related group weight index) compared with white pediatric patients.

Our study suggests inequities in DRG prospective hospital payment vis-à-vis pediatric minority Americans (as measured at one large northeastern academic medical center).

There are a number of components of DRG hospital payment in the federal Medicare system that are likely to affect the minority pediatric patient. These include the "disproportionate share adjustment" (ie, additional payments made to hospitals that treat poor patients), and "outlier payment" (ie, additional payment for very expensive pa-

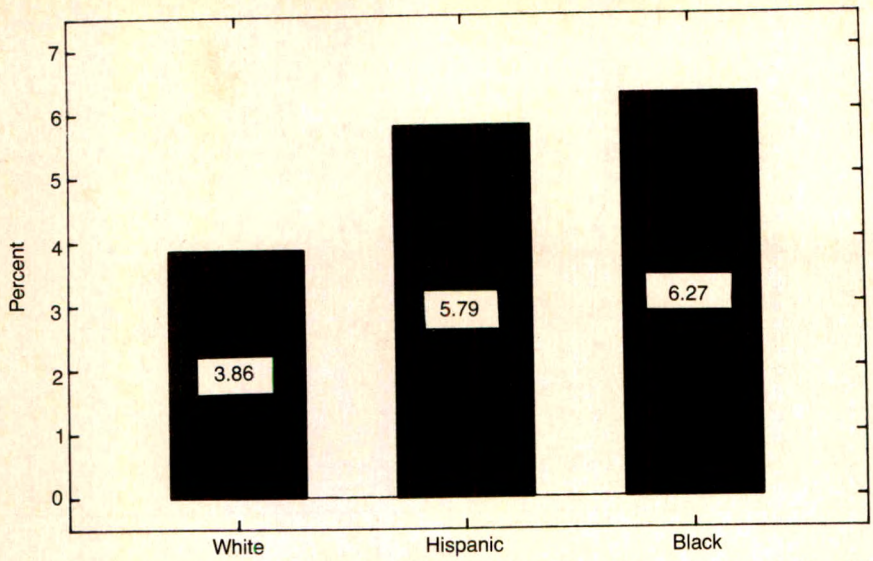


Fig 2.—The percentage of outliers was higher for black ($P<.0001$) and Hispanic ($P=.01$) pediatric patients compared with white pediatric patients.

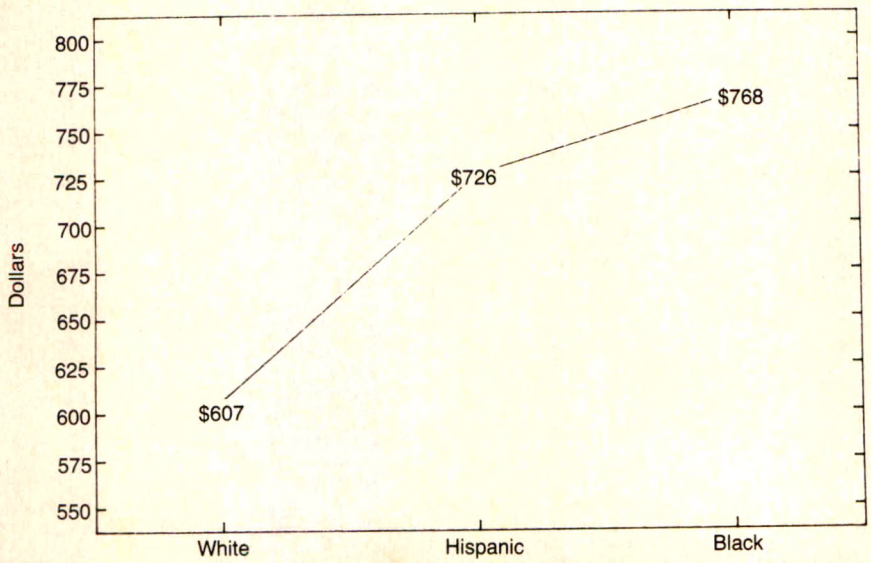


Fig 3.—The mean diagnostic cost per patient (adjusted for diagnosis related group weight index) was significantly higher for black ($P<.0001$) and Hispanic ($P<.009$) pediatric patients compared with white pediatric patients.

tients); outlier payment was originally based principally on the hospital length of stay (ie, the number of days in the hospital). In addition, teaching hospitals (many of which deliver a substantial proportion of care to black and Hispanic pediatric patients) also receive a "teaching adjustment" (ie, additional payment for teaching costs). The federal Medicare DRG prospective payment system gave substantial consideration to the additional hospital resource requirements of minority Americans. However, recent changes at the federal level may reduce the payment for certain groups of minority pediatric patients. Both the Health Care Financing Administration and the Prospective Payment Assessment Commission have recommended changes in outlier methodology (ie, very expensive patients) at the federal level that may reduce payment to public hospitals (those that care for a great number of pediatric black or Hispanic patients).[2] Most all payer DRG systems use the federal system as their model.

In the present study we used race and ethnic origin as criteria for segmenting populations and comparing hospital-use data. In doing so, we have unintentionally perpetuated the misconception common in our society that, because of race or ethnic background alone, there are intrinsic hospital resource differences. In fact this is not the case. Minority populations have differences in health status because of a variety of economic forces, educational factors, and social factors associated with poverty. No doubt black and Hispanic patients' greater hospital resource use was not related to skin color or ethnic background, but to these socioeconomic causative factors. Nonetheless, our analysis suggests that minority populations may present the "average" hospital in America with more financial risk than the "average" patient in general.

As the federal DRG prospective payment system enters its sixth year, a number of potential changes to prospective payment systems may affect the financial position of hospitals in regard to pediatric minority patients. Teaching adjustments for hospitals are under scrutiny and are being decreased (in particular, the indirect teaching payment). Some question has been raised at the health policy level concerning the current level of the disproportionate share adjustment for hospitals (ie, payment for treating poor patients), with a possible "reexamination" of this adjustment. If these types of changes are translated to state-based DRG all payer systems, pediatric minority patients could be substantially effected.

There is a growing need for the pediatric medical community to become involved in the creation of health care policy. It appears that politicians and legislators are likely to push for "comprehensive cost-effective" medical and pediatric care for all. Health care financing will be used to direct both health care provision and health care policy for pediatric patients. The present study demonstrates that certain groups of pediatric patients may be "vulnerable" under DRG prospective payment. Attention should be directed to assessing these patients' continued access to quality medical care.

This project was sponsored (in part) by the Association of Puerto Ricans in Science and Engineering, New York, NY.

Editorial critique and encouragement were provided by the late Ira M. Teicher, MD, Surgical Education, LIJMC; Gordon Doletto and James Moyer, Division of Management Information Systems and the DRG Task Force, LIJMC, provided computer-programming assistance; and Christina Weiss prepared the manuscript.

References

1. Iglehart JD. Medicare begins prospective payment for hospitals. *N Engl J Med.* 1983; 308:1428-1432.

2. Department of Health and Human Services, Medicare Program: Changes to the inpatient hospital prospective payment system and fiscal year 1989 rates; proposed rule. *Federal Register.* May 27, 1988;53:103:19497-19686.

3. Munoz E, Soldano R, Gross H, et al. DRGs and the transfer of surgical patients between hospitals. *Arch Surg.* 1988;123:68-71.

4. Feder J, Hadley J, Zuckerman S. How did Medicare's prospective payment system affect hospitals? *N Engl J Med.* 1988;317:867-873.

5. McCarthy CM. DRGs: Five years later. *N Engl J Med.* 1988;318:1683-1686.

6. Munoz E, Laughlin A, Regan DM, et al. The financial effect of emergency room admissions under prospective payment systems. *JAMA.* 1985; 254:1763-1771.

7. Munoz E, Soldano R, Gross H, et al. DRGs and the transfer of surgical patients between hospitals. *Arch Surg.* 1988;123;68-71.

8. Munoz E, Sterman H, Cohen Jr, et al. Financial risk, hospital cost, complications and comorbidities (CCs) in surgical non-CC stratified DRGs. *Ann Surg.* 1988;207:305-309.

9. Horn SD. Measuring severity of illness comparisons across institutions. *Am J Public Health.* 1983;73:35-31.

10. Epstein EM, Stern RS, Tognetti J, et al. The association of patients socioeconomic characteristics with the length of hospital stay and hospital charges with DRGs. *N Engl J Med.* 1988;318:1579-1585.

11. Munoz E, Regan DM, Margolis IB, et al. Surgonomics: the identifier concept: hospital charges in general surgery and surgical specialities under prospective payment systems. *Ann Surg.* 1985;202:119-125.

12. Munoz E. The cost dynamics of emergency hospitalized patients. *Emergency Med Serv.* In press.

Book Review

Books Received but Not Reviewed

Adolescent Oncology, by C. K. Tebbi, 556 pp, $65, London, England, Futura Publishing Co Inc, 1987.

Adopting From Latin America, by James Pahz, 189 pp, $31.75, Springfield, Ill, Charles C Thomas Publisher, 1988.

Advances in Neuroblastoma Research 2, edited by Audrey Evans, 260 pp, $130, New York, NY, Alan R Liss Inc, 1988.

The Aids Challenge Prevention Education for Young People, by M. Quackenbush, M. Nelson, K. Clark, 542 pp, $24.95, Santa Cruz, Calif, Network Publications, 1988.

Allergic Diseases From Infancy to Adulthood, by C. W. Bierman, D. S. Quinton, 848 pp, $95, Philadelphia, Pa, WB Saunders Co, 1988.

Allergy (An International Textbook), edited by M. H. Lessof, T. H. Lee, D. M. Kemeny, 678 pp, $69.50, Baltimore, Md, Williams & Wilkins, 1988.

Allergy Principles and Practice, Volumes I and II, edited by Elliot Middleton Jr, C. E. Reed, E. F. Ellis, N. F. Adkinson, J. W. Yunginger, 1699 pp, St Louis, Mo, CV Mosby Co, 1988.

The Art of Scientific Writing, by Hans Ebel, C. Bliefert, W. E. Russey, 493 pp, $24.95, New York, NY, VCH Publishers Inc, 1987.

Assisted Ventilation of the Neonate, by Jay Goldsmith, E. Karotkin, 490 pp, $55, Philadelphia, Pa, WB Saunders Co, 1988.

Asthma: The Facts, by Donald Lane, Anthony Storr, 193 pp, $18.95, New York, NY, Oxford University Press Inc, 1987.

Attention Deficit Disorders, Hyperactivity and Associated Disorders, by Wendy Coleman, 79 pp, $5.50, Madison, Wis, Calliope Books, 1988.

Basic Child Psychiatry, by Philip Barker, 425 pp, Boston, Mass, Blackwell Scientific Publications Inc, 1988.

Behavior of the Growth Plate, edited by Hans Uhthoff, J. J. Wiley, 433 pp, $99, New York, NY, Raven Press, 1988.

Bringing Out the Best in Your Baby, by Art Ulene, S. Shelov, 313 pp, $3.95, New York, NY, Macmillan Publishing Co Inc, 1988.

Cardiovascular Diseases, by H. S. Rosenberg, J. Bernstein, 172 pp, $132, New York, NY, S Karger AG, 1988.

Care of the Newborn, by R. Schreiner, N. Bradburn, 215 pp, $38, New York, NY, Raven Press, 1987.

Cellular and Molecular Basis of Cystic Fibrosis, edited by G. Mastella, P. M. Quinton, 489 pp, $40, San Francisco, Calif, San Francisco Press, 1988.

The Cerebral Palsies of Children, by Sir William Osler, 92 pp, $39, Philadelphia, Pa, JB Lippincott, 1988.

Cerebrospinal Fluid and the Brain Edemas, by T. H. Milhorat, 136 pp, $45, New York, NY, Neuroscience Society, 1987.

The Chief Resident as Manager, by Neil Whitman, E. Weiss, L. Lutz, 151 pp, $16, Salt Lake City, University of Utah School of Medicine, 1988.

Child Health in a Changing Society, by John Forfar, 312 pp, $19.95, New York, NY, Oxford University Press, 1988.

Childhood Constipation and Soiling, by Wynne McCain, 64 pp, $6.95, Minneapolis, Minn, Minneapolis Children's Medical Center, 1988.

Children and Adolescents With Mental Illness, by Evelyn McElroy, 220 pp, $12.95, Kensington, England, Woodbine House, 1987.

Children With Asthma: A Manual for Parents, by Thomas Plaut, 291 pp, $11.95, Amherst, Mass, Pedipress Inc, 1987.

Children With Epilepsy: A Parents Guide, by H. Reisner, 314 pp, $12.95, Kensington, England, Woodbine House, 1988.

Choices for a Hearty Heart, by J. C. Piscatella, 592 pp, $14.95, New York, NY, Workman Publishing Co, 1987.

Clinical Paediatric Surgery, by P. G. Jones, A. A. Woodward, 588 pp, Boston, Mass, Blackwell Scientific Publications, 1986.

Craig's Care of the Newly Born Infant, by T. L. Turner, Jean Douglas, F. Cockburn, 194 pp, $36, White Plains, NY, Longman Inc, 1988.

Current Therapy in Pediatric Infectious Disease 2, by J. D. Nelson, 407 pp, Philadelphia, Pa, BC Decker Inc, 1988.

Developmental and Neonatal Hematology, by J. A. Stockman, C. Pochedly, 348 pp, $69, New York, NY, Raven Press, 1988.

Diagnosis and Management of Renal Disease and Hypertension, by Anil K. Mandal, 540 pp, $67.50, Philadelphia, Pa, Lea & Febiger, 1988.

Diagnostic Imaging in Paediatrics, by Isky Gordon, 298 pp, $79.50, Dobbs Ferry, NY, Sheridan House Inc, 1987.

Diseases of the Colon, Rectum and Anal Canal, by Joseph Kirsner, R. Shorter, 739 pp, $115, Baltimore, Md, Williams & Wilkins, 1988.

Does AIDS Hurt: Educating Young Children About AIDS, by M. Quackenbush, S. Villareal, 162 pp, $14.95, Santa Cruz, Calif, Network Publications, 1988.

Doppler Ultrasound Measurement of Maternal-Fetal Hemodynamics, by D. Maulik, D. McNellis, 320 pp, Ithaca, NY, Perinatology Press, 1987.

Early Vascular Complications in Children With Diabetes, by B. Weber, 284 pp, $142.75, New York, NY, S Karger AG, 1988.

Essential and Toxic Trace Elements in Human Health and Disease, by Ananda S. Prasad, 328 pp, $95, New York, NY, Alan R Liss Inc, 1988.

Essentials of Neonatal Medicine, by M. I. Levene, D. Tudehope, J. Thearle, 411 pp, Boston, Mass, Blackwell Scientific Publications, 1988.

Food Allergies (A Primer for People), by S. Allan Bock, 87 pp, $8.95, New York, NY, Vantage Press Inc, 1988.

Food Allergy, edited by Dietrich Reinhardt, E. Schmidt, 319 pp, $49, New York, NY, Raven Press, 1988.

Genetics and Epithelial Cell Dysfunction in Cystic Fibrosis, by J. R. Riordan, M. Buchwald, 240 pp, $46, New York, NY, Alan R Liss Inc, 1987.

Gilles de la Tourette Syndrome, by A. K. Shapiro, J. Young, T. Feinberg, 584 pp, $70, New York, NY, Raven Press, 1988.

The Growing Years, by M. Rubenstein, 416 pp, $22.95, New York, NY, Atheneum Publishers, 1988.

Handicapped Children and Youth, by H. Wallace, R. Biehl, L. Taft, A. Oglesby, 378 pp, $39.95, New York, NY, Human Sciences Press, 1987.

Hemostatic Disorders of the Pregnant Woman and Newborn Infant, by W. E. Hathaway, J. Bonnar, 233 pp, $45, New York, NY, John Wiley & Sons Inc, 1987.

Acute Systemic Organ Injury in Term Infants After Asphyxia

J. M. Perlman, MD; E. D. Tack, MD; T. Martin, MD; G. Shackelford, MD; E. Amon, MD

• The systemic manifestations of "asphyxia" were evaluated prospectively in 35 consecutively intubated term newborn infants. The following systemic organ injuries were identified most often: (1) renal, ie, oliguria less than 1 mL/kg per hour for at least 24 hours (40%), an elevated urinary β-2-microglobulin concentration (57%), azotemia (11%), and an elevated serum creatinine level (17%); (2) central nervous system, ie, hypoxic-ischemic encephalopathy (including seizures) (31%) or an abnormal cranial ultrasound scan, ie, diffuse parenchymal echogenicity, slitlike ventricles, and poor visualization of the sulci, and/or intracranial hemorrhage (26%); (3) cardiovascular, ie, an abnormal echocardiogram (25%) or abnormal electrocardiogram (11%); (4) pulmonary complications, including persistent pulmonary hypertension (23%); and (5) gastrointestinal complications, which were rare. Traditional markers of fetal distress were not related to the frequency and/or distribution of systemic organ injury. An important implication of this study relates to the recognition of the extent and distribution of organ injury in the "asphyxiated" infant.

(*AJDC.* 1989;143:617-620)

The circulatory response to intrauterine asphyxia in the experimental animal results in a redistribution of cardiac output with a larger proportion of flow distributed to the cerebral, coronary, and adrenal circulations and with decreased perfusion to the kidney, gastrointestinal tract, and skin.[1-3] The consequence of decreased perfusion and such other concomitants of asphyxia, ie, hypercarbia, acidosis, and alterations of cellular integrity, may be organ injury of a severity that is determined in part by the duration of an insult and by the adaptive ability of the fetus to respond to further insult. The frequency and extent of systemic organ injury in the asphyxiated newborn infant is ill defined.[4] An understanding of organ injury may provide insight with regard to the fetal response and/or vulnerability to intrauterine hypoxia. The objective of this prospective study was to determine the frequency and severity of acute systemic organ injury in the term infant after perinatal asphyxia.

Accepted for publication December 21, 1988.

From the Edward Mallinckrodt Department of Pediatrics, Divisions of Newborn Medicine (Dr Perlman and Dr Tack) and Cardiology (Dr Martin), Edward Mallinckrodt Department of Radiology (Dr Shackelford), and the Department of Obstetrics/Gynecology (Dr Amon), Washington University School of Medicine, St Louis, Mo.

Reprint requests to Children's Hospital, Division of Newborn Medicine, 400 S Kingshighway, St Louis, MO 63110 (Dr Perlman).

PATIENTS AND METHODS

Patients

The study population comprised 35 consecutive intubated, "asphyxiated" term infants with a mean (±SD) birth weight of 3193±768 g and a mean (±SD) gestational age of 40±1.9 weeks who were admitted to the Newborn Intensive Care Unit at Children's Hospital, St Louis, Mo, between July 1, 1985, and May 1, 1986. *Asphyxia* was prospectively defined as follows: (1) a 5-minute Apgar score of 5 or less in initially nonintubated or intubated infants; (2) a 5-minute Apgar score of 6 in intubated infants (infants were entered in this category if an Apgar respiratory score of 2 had been assigned because with tube placement we consider such a respiratory score to be an overestimation); and/or (3) an umbilical cord arterial pH of less than 7.20, or an umbilical cord arterial P_{CO_2} exceeding 50 mm Hg.

Protocol

Data obtained from the medical records of each of the 35 infants were derived from a detailed review of the obstetrical record, the delivery room management, and the postnatal clinical history, including daily recordings of urine output, serum electrolyte determinations, and levels of serum calcium, blood glucose, serum urea nitrogen, and serum creatinine. Assessment of gestational age was made by the criteria of Dubowitz et al.[5]

Identification of systemic abnormalities was performed as follows:

1. Renal evaluation included a first-void urine sample (before the initiation of antibiotic therapy) for the determination of β-2-microglobulin (B_2M) and creatinine concentrations and the hourly determination of urine output. The B_2M concentrations were measured in duplicate by radioimmunoassay (Pharmacia Diagnostic, Uppsala, Sweden). The reproducibility of B_2M measurements in our laboratory is ±4.8%.[6] The 95% confidence limit (mean±SD) for urinary B_2M in healthy infants in our laboratory is 4 mg/L.[6,7] *Azotemia* was defined as a serum urea nitrogen concentration greater than 710 mmol/L of urea, and a serum creatinine level of greater than 90 μmol/L after the third day was considered abnormal. *Oliguria* was defined as a urine output of less than 1 mL/kg per hour, and retrospectively was categorized further as being *transient* if it was present in the first 24 hours of life only, but with normal urine output by age 36 hours, or *persistent* if it was present for the first 36 hours of life.

2. Results of a neurologic evaluation were considered abnormal if (1) clinical abnormalities such as hypotonia, stupor, coma, and seizures were detected at the examination[8] or (2) the cranial ultrasound scan showed evidence of intraventricular hemorrhage or intraparenchymal echodensity. Parenchymal abnormalities were considered if there was diffuse echogenicity of the kind that is often associated with slitlike ventricles and poorly visualized sulci.[9] Scans were performed in the first 2 days of life as part of the study. Additional scans were performed as clinically indicated as part of routine care. Interpretation of scans were made by one of us (G.S.) without knowledge of the clinical status of the infants.

3. Cardiac evaluation included (1) a 12-lead electrocardiogram, (2) an M-mode echocardiogram, and (3) a two-dimensional echocardiogram with Doppler interrogation. These studies were performed in the first 2 days of life. Cardiac measurements obtained by M-mode echocardiogram used accepted standards.[10-13] Abnormalities were diagnosed when values deviated more than 2 SDs from the mean values in normal infants.

Two-dimensional echocardiograms with Doppler interrogation were performed in the first 4 days of life in 15 patients when this technique became available. Measurement of ventricular dimensions and functional criteria was performed on M-mode recordings. Qualitative estimates of abnormalities were made from two-dimensional recordings according to accepted standards.[14,15] Recordings were made on videotape for later review.

Electrocardiograms were interpreted by established criteria for term infants.[16] Abnormalities in axis and voltage were detected if the axis or voltage was greater than 2 SDs from normal. Interpretation of the scans was done by one of us (T.M.) without prior knowledge of the clinical status of the infant.

4. Pulmonary disease was considered important if the infant required intubation for more than 48 hours. Persistent pulmonary

hypertension was defined as persistent hypoxemia (Po_2 <60 mm Hg) despite hyperventilation with no evidence of pulmonary or cardiac pathologic disorder.[17]

5. Gastrointestinal complications were considered if there was evidence of necrotizing enterocolitis.[18] Informed parental consent was obtained for each infant before entry into the study, which was approved by the institutional review board of Washington University, St Louis, Mo.

Statistical Analysis

χ^2 Analysis was used to assess the relationship of perinatal factors (ie, fetal heart monitoring, type of delivery, cord blood measures, Apgar score, gestational age, and birth weight) to outcome. If the dependent or independent variable was continuous while the other was dichotomous, *t* tests were used. Polynomial regression was used to examine relationships between continuous variables.

RESULTS

Characteristics of Patient Population

Obstetric.—The pregnancy was complicated in 24 (70%) of the 35 infants, most frequently by pregnancy-induced hypertension (40%), limited or no prenatal care (20%), gestational diabetes (12%), or other factors (28%).

Labor and Delivery.—Twenty-eight (80%) of the 35 infants were born at our institution, while 7 (20%) were not. The labor was complicated by an abnormal fetal heart rate tracing in 18 (70%) of the 26 cases; abnormalities included tachycardia (heart rate >160 beats per minute) (n=2), late decelerations (n=8), bradycardia (heart rate <80 beats per minute) (n=7), and a sinusoidal pattern (n=1). Fifty percent of the deliveries were via emergency cesarean section, 25% were vaginal, 20% were via either forceps or vacuum extraction, and 5% were via an elective cesarean section.

Postnatal.—Six of the infants had an Apgar score of 6 at 5 minutes, 2 infants with an Apgar score of 7 or greater were enrolled because of an abnormal cord arterial blood P_{CO_2} and pH, and the remaining 30 infants had an Apgar score of 5 or less. The mean umbilical cord arterial pH was 7.11±0.14, the P_{CO_2} was 73±36 mm Hg, and the base excess was 15±6. There was no relationship between the 5-minute Apgar score and cord arterial blood pH, P_{CO_2}, and base excess ($P>.05$).

All 35 infants were intubated while in the delivery room. Seven of the infants required cardiopulmonary resuscitation in the delivery room, ie, chest compression and epinephrine (n=6) or chest compression alone (n=1). Two of the 35 infants died on the second postnatal day.

Organ Injury in Asphyxiated Infants

Twelve (34%) of the 35 infants had no evidence of organ injury. Eight infants (23%) had an abnormality that was confined to one organ. Thus, 5 infants had only renal abnormalities, ie, transient oliguria with an elevated B_2M concentration, and 3 infants had only central nervous system abnormalities, ie, clinical signs of hypoxic-ischemic encephalopathy (n=3). Twelve (34%) of the infants had an abnormality that involved two organs. In 5 of the 12 infants the abnormalities were confined to the kidneys (persistent oliguria with an elevated B_2M level) and central nervous system (clinical signs of hypoxic-ischemic encephalopathy). In 4 of the 12 infants the abnormalities were confined to the heart (right ventricular dysfunction, ie, dilated right ventricle with high-velocity tricuspid regurgitation and atrial shunting) and lung (respiratory distress requiring medical management, ie, hyperventilation for >72 hours). In 2 of the 12 infants the abnormalities were confined to the heart (left ventricular dysfunction, 2 patients) and brain (intracranial hemorrhage, 2 patients). In 1 infant the abnormalities were confined to the kidney (transient oliguria) and heart (right ventricular dysfunction, as described above).

Three infants (9%) had organ abnormalities that involved three organs. The organs affected were the kidneys, ie, oliguria with an elevated B_2M concentration; heart, ie, right ventricular dysfunction (as described above in two patients) and biventricular dysfunction (in one patient); and central nervous system injury (clinical signs of hypoxic-ischemic encephalopathy in all three cases).

The frequency of specific organ injury was next evaluated. Abnormalities of renal function occurred most commonly. Thus, clinical abnormalities, ie, oliguria (transient, n=8; persistent, n=6), occurred in 14 infants (40%); an elevated B_2M concentration in the first-void urine was noted in 20 infants (57%) (this to a mean [±SD] value of 16.5±11 mg/L) ($P<.001$ compared with normal). Serum abnormalities, ie, azotemia and an elevated serum creatinine level, were noted in 4 (11%) and 6 (17%) infants, respectively.

Central nervous system abnormalities were observed in 13 (37%) of the infants. All 13 infants presented with clinical signs consistent with hypoxic-ischemic encephalopathy. In 6 of the 13 infants, the ultrasound scan disclosed increased parenchymal echogenicity with slitlike ventricles and poor visualization of the sulci. Three of the 13 infants had evidence of intracranial hemorrhage, ie, epidural hemorrhage in 1 infant and a posterior fossa hemorrhage in 2 infants (all 3 lesions were confirmed by computed tomography). Four of the 13 infants had normal ultrasound scans.

Cardiac abnormalities were observed in 10 (28%) of the infants. The two-dimensional echocardiogram disclosed a dilated right ventricle with high-velocity tricuspid regurgitation and atrial shunting in 6 infants and a dilated right ventricle only in 1 infant. M-mode echocardiography demonstrated left ventricular abnormalities in 3 infants. The electrocardiogram was abnormal in 4 (8%) infants with biventricular hypertrophy (n=2), left ventricular hypertrophy (n=1), and right ventricular hypertrophy (n=1) (all 4 had echocardiographic findings).

All of the infants were intubated in the delivery room and then transferred to the intensive care unit. Indications for intubation included the following: (1) evaluation of the upper airways for the presence of meconium (n=14); (2) minimal or no respiratory effort (n=12); and (3) respiratory distress (n=9). Fourteen (40%) of the infants were extubated within 12 hours; 6 additional infants (17%) were extubated within 24 hours; 3 infants (8%) were extubated by 36 hours of life; 2 infants were extubated by 48 hours; and 2 infants died during the second postnatal day. Eight (23%) of the 35 infants required intubation for longer than 72 hours. Four of these infants exhibited findings consistent with persistent pulmonary hypertension; 2 of the 4 infants required extracorporeal membrane oxygenation.

Gastrointestinal symptoms were rare; one infant developed a jejunal perforation on the fourth postnatal day

Organ Injury in Infants by Various Criteria*

Organ Involvement	Apgar Score 5 min 4-6 (n=21)	Apgar Score 5 min <4 (n=14)	10 min, <5 (n=9)	MSAF (n=12)	CPR (n=7)
Renal					
Elevated B_2M	11	9	7	10	4
Oliguria					
Persistent	1	5	5	2	3
Transient	6	2	1	3	1
Central nervous system					
HIE including seizures	7	6	6	3	6
Abnormal ultrasonography	3	6	5	3	5
Cardiac	7	3	1	4	0
Pulmonary	6	2	1	4	0

*MSAF indicates meconium-stained amniotic fluid; HIE, hypoxic-ischemic encephalopathy; CPR, cardiopulmonary resuscitation; and B_2M, β-2-microglobulin.

without histologic evidence of colitis.

When the data were analyzed, there was no relationship between obstetrical variables, the Apgar score, cord arterial blood P_{O_2}, P_{CO_2}, pH, or base excess, and organ injury. A significant relationship was noted between the 5-minute Apgar score and the requirement for Ringer's lactate ($P<.02$, $r=44$).

The data were categorized further with regard to acute organ injury in the 35 infants who met the following criteria: (1) an Apgar score of 4 to 6 at 5 minutes, (2) an Apgar score of less than 4 at 5 minutes, (3) an Apgar score less than 5 at 10 minutes, (4) the need for delivery room cardiopulmonary resuscitation, and (5) the presence of meconium-stained amniotic fluid (Table). Specifically, evidence of hypoxic-ischemic encephalopathy, including seizures and oliguria, was more common in infants with prolonged low Apgar scores and in infants requiring cardiopulmonary resuscitation. Cardiopulmonary disease was most frequently observed in infants with meconium-stained amniotic fluid.

COMMENT

The present data demonstrate the frequent occurrence of organ injury in the sick, "asphyxiated" term infant in the immediate perinatal period. Thus, single or multiple organ injuries were observed in approximately 70% of the infants. Renal abnormalities were the most frequent findings, occurring in approximately 50% of the infants; central nervous system abnormalities occurred in one third of infants; and cardiovascular and pulmonary abnormalities occurred in 25% of infants. In contrast, gastrointestinal tract abnormalities were rare.

The frequent occurrence of renal injury in these infants may be in part the consequence of the adaptive response of the fetus to intrauterine hypoxia.[1-3] Thus, with fetal hypoxia, blood flow to the kidney is reduced to maintain perfusion of the heart, brain, and adrenal glands. The proximal renal tubule is vulnerable to such a reduction in blood flow.[19,20] Coupled with other concomitants of asphyxia, ie, hypercarbia, acidosis, and alterations in cellular integrity, if the decrease in renal perfusion is marked, necrosis of tubular epithelial cells may occur, resulting in the clinical syndrome of acute tubular necrosis.[20] In contrast, a less severe alteration in perfusion will result in more subtle injury. Such subtle injury can be detected by the urinary concentration of B_2M, which is a low-molecular-weight protein freely filtered through the glomerulus.[21] The vast majority of this filtered protein is reabsorbed in the proximal tubules of the kidneys, even in immature kidneys that produce little or no protein normally detectable in the urine.[22-24] Injury to the proximal tubule results in markedly elevated concentrations of B_2M in the urine. Thus, measurement of urinary levels of this protein provides a sensitive indicator of proximal tubular function.[7,25] Indeed, in otherwise-healthy term infants with meconium-stained amniotic fluid who exhibited elevated urinary B_2M concentrations, we have demonstrated proximal tubular injury when these infants were compared with healthy term infants with clear amniotic fluid.[6]

Central nervous system abnormalities were observed in 30% of the infants. Clinical findings consistent with hypoxic-ischemic encephalopathy, ie, seizures, stupor, and/or coma, occurred most frequently in those infants with a prolonged low Apgar score or in infants requiring cardiopulmonary resuscitation. The observation that a prolonged low Apgar score is associated with increased risk for seizures is consistent with previous reports.[8,26] Ultrasonographic abnormalities were noted in 25% of cases. The most common abnormality was increased parenchymal echogenicity with poorly visualized sulci, a finding we have previously demonstrated in infants with hypoxic-ischemic cerebral injury.[9,27] Intracranial hemorrhage was a less frequent finding and had unusual locations, ie, the posterior fossa and epidural space.

Abnormalities on cardiac evaluation were noted in approximately 25% of the infants and affected both right and left ventricular function. The abnormal findings are consistent with those reported by others.[28-31] Abnormalities that were considered to be secondary to ischemic injury (ie, left ventricular dilatation or dysfunction) were infrequent, occurring in less than 10% of the infants. Although M-mode echocardiography has been the standard instrument for studying ventricular function abnormalities in infants,[10-13] it may be unable to detect ischemic cardiomyopathy. Segmental wall-motion abnormalities may be overlooked. In addition, assumptions concerning homogenicity of wall motion in newborn infants may not be justified.[32] The two-dimensional echocardiogram is a more sensitive measure with regard to the detection of right ventricular dysfunction,[14,15] and perhaps left ventricular dysfunction as well.[32] Indeed, of the 15 infants who underwent Doppler examination, 30% exhibited right-sided abnormalities.

Although all infants were intubated while in the delivery room, more than 50% were extubated within 24 hours. The most common reason for intubation was to clear the airway of meconium by suction. One third of the infants failed to initiate or had minimal respiratory activity; however, only one infant failed to

exhibit spontaneous respirations by 5 minutes and this infant died on the second postnatal day. The need for prolonged ventilatory support was invariably accompanied by clinical findings consistent with persistent pulmonary hypertension. This occurred more frequently in the infants with a history of meconium-stained amniotic fluid. Whether the observed pulmonary hypertension was indicative of an acute or chronic process is unclear from the available data.

Gastrointestinal symptoms were surprisingly rare. One possible explanation for the paucity of findings may be that before enteral feedings were initiated, the sickest infants were given parenteral alimentation until their conditions were clinically stable.

No relationship could be established between specific organ dysfunction and perinatal events such as fetal heart monitoring abnormalities, arterial oxygen, pH, and base excess, and Apgar score. Moreover, no relationship was noted between the 5-minute Apgar score and acid-base status, a finding consistent with previous reports.[33-35] It could be argued that this lack of a relationship might reflect the entry criteria used to define asphyxia in the present study. It should be noted, however, that these criteria are consistent with those commonly used previously to define asphyxia.[8,26] However, this discordant relationship should not be an unexpected finding since a criterion such as the 5-minute Apgar score is a "window" in time and does not reflect the duration of the insult or the adaptive response of the fetus to preserve organ integrity. In the present study, a prolonged low Apgar score or the need for cardiopulmonary resuscitation in the delivery room was invariably associated with clinical signs of hypoxic-ischemic encephalopathy, including seizures, oliguria, and death, suggesting a maladaptive circulatory response with decreased perfusion to the brain and kidney. In contrast, infants with meconium-stained amniotic fluid with similarly low Apgar scores exhibited frequent cardiac and proximal tubular injury, with neurologic abnormalities occurring less frequently, suggesting preservation of central nervous system perfusion.

Our data differ from those of Sexson et al,[4] who similarly studied system organ injury in asphyxiated term infants. In that report pulmonary involvement was a frequent finding with renal injury an uncommon finding. The differences between the two studies may in part reflect methodology and the definition of disease.

An important implication of the present study relates to the recognition of the extent of organ injury in the "asphyxiated infant." Thus, multiple organ injury was noted in one half of the infants. The frequent renal injury may have important implications regarding the fluid and electrolyte management of such patients; the relatively common cardiac dysfunction may be an important contributing factor to the respiratory distress observed in such infants. Moreover, these data indicate that traditional markers of fetal distress are relatively poor indicators of the frequency and distribution of systemic organ injury.

This study was supported in part by GCRC NIH RR00036 (Mr Perlman).

Charles C. T. Chang, MS, and Cathy Hausel, RN, provided technical assistance in performing the B_2M determinations.

References

1. Behrman RE, Lees MH, Petersen EH, Lannoy CW, Seeds AE. Distribution of the circulation in the normal and asphyxiated fetal primate. *Am J Obstet Gynecol.* 1970;180:956-961.

2. Cohn EH, Sack SEJ, Heymann MA, Rudolph AM. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol.* 1974;120:817-824.

3. Rudolph AM: The fetal circulation and its response to stress. *J Dev Physiol.* 1984;6:11-16.

4. Sexson WR, Sexson SB, Rawson JE, Brann AW. The multisystem involvement of the asphyxiated newborn. *Pediatr Res.* 1976;10:432. Abstract.

5. Dubowitz L, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr.* 1970;77:1-5.

6. Cole JW, Portman RJ, Lim Y, Perlman JM, Robson AM. Urinary B_2-microglobulin in full term newborns: evidence for proximal tubular dysfunction in infants with meconium-stained amniotic fluid. *Pediatrics.* 1985;76:958-964.

7. Tack ED, Perlman JM, Robson AM. Renal injury in sick newborn infants: a prospective evaluation utilizing urinary B_2-microglobulin concentrations. *Pediatrics.* 1988;81:432-440.

8. Volpe JJ: *Neurology of the Newborn.* 2nd ed. Philadelphia, Pa: WB Saunders Co; 1987.

9. Siegel MJ, Shackelford GD, Perlman JM, Fulling GE. Hypoxic-ischemic encephalopathy in term infants: diagnosis and prognosis evaluated by ultrasound. *Radiology.* 1984;152:395-399.

10. Sahn DJ, DeMaria AN, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation.* 1978; 58:1072-1083.

11. Johnson GL, Breart GL, Gewitz MH, et al. Echocardiographic characteristics of premature infants with patent ductus arteriosus. *Pediatrics.* 1983;72:864-871.

12. Hirschfeld S, Meyer R, Schwartz DC, Korfhagen J, Kaplan S. Measurement of right and left ventricular systolic time intervals by echocardiography. *Circulation.* 1975;51:304-309.

13. Spodick DH, Ball HE, Pigott VM. Effects of recording speed on precision of time-based polycardiographic measurements. *Br Heart J.* 1978; 40:13441348.

14. Goldberg SJ, Allen HD, Sahn DJ. *Pediatric and Adolescent Echocardiography: A Handbook.* Chicago, Ill: Year Book Medical Publishers Inc; 1980.

15. Goldberg SJ, Allen HD, Marx GR, Flynn C. *Doppler Echocardiography.* Philadelphia, Pa: Lea & Febiger; 1985.

16. Leibman J. Electrocardiography. In: Moss AJ, Adams FH, Emmanouilides GG, eds. *Electrocardiography in Heart Disease in Infants, Children, and Adolescents.* 2nd ed. Baltimore, Md: Williams & Wilkins; 1977.

17. Fox WW, Duara S. Persistent pulmonary hypertension in the neonate: diagnosis and management. *J Pediatr.* 1983;103:505-514.

18. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am.* 1986;33:179-201.

19. Dauber IM, Krauss AN, Symchych PS, Auld PAM. Renal failure following perinatal anoxia. *J Pediatr.* 1976;88:851-855.

20. Stark H, Geiger R. Renal tubular dysfunction following vascular accidents of the kidneys in the newborn period. *J Pediatr.* 1973;83:933-940

21. Stites DP, Pawlak LL, Carr MC, Fudenberg HH, Poulik MD. Ontogeny of beta-2-microglobulin synthesis in the human fetus. *Dev Comp Immunol.* 1978;2:185-192.

22. Takieddine F, Tabbara M, Hall P, Sokol RJ, King KC. Fetal renal maturation: studies on urinary B_2-microglobulin in the neonate. *Acta Obstet Gynecol Scand.* 1983;62:311-314.

23. Aperia A, Broberger O, Elinder G, Herin P, Zetterstrom R. Postnatal development of renal function in pre-term and full-term infants. *Acta Pediatr Scand.* 1981;70:183-187.

24. Assadi FK, John EG, Justice P, Fornell L. Beta-2-microglobulin clearance in neonates: index of tubular maturation. *Kidney Int.* 1985;28: 153-157.

25. Aperia A, Broberger O. Beta-2-microglobulin, an indicator of renal tubular maturation and dysfunction in the newborn. *Acta Pediatr Scand.* 1979; 68:669-676.

26. Nelson KB, Ellenberg JH. Neonatal signs as predictors of cerebral palsy. *Pediatrics.* 1979; 64:225-232.

27. Perlman JM, Tack ED. Renal injury in the asphyxiated newborn infant: relationship to neurological outcome. *J Pediatr.* 1988;113:875-879.

28. Bucciarelli RL, Nelson RM, Egan EA, Eitzman DV, Gessner IH. Transient tricuspid insufficiency of the newborn: a form of myocardial dysfunction in stressed newborns. Pediatrics. 1977;59:330-337.

29. Cabal LA, Devaskar U, Siassi B, Hodgman JE, Emmanouilides G. Cardiogenic shock associated with perinatal asphyxia in preterm infants. *J Pediatr.* 1980;96:705-710.

30. Donnelly WH, Bucciarelli RL, Nelson RM. Ischemic papillary muscle necrosis in stressed newborn infants. *J Pediatr.* 1980;96:295-300.

31. Finley JP, Howman-Giles RB, Gilday DL, Bloom KR, Rowe RD. Transient myocardial ischemia of the newborn infant demonstrated by thallium myocardial imaging. *J Pediatr.* 1979; 94:263-270.

32. Rein AJ, Sanders SP, Colan SD, Parness IA, Epstein M. Left ventricular mechanics in the normal newborn. *Circulation.* 1987;76:1029-1036.

33. Sykes GS, Molloy PM, Johnson P, Wei G, Ashworth F, Stirrat GM. Do Apgar scores indicate asphyxia? *Lancet.* 1982;1:494-496.

34. Silverman F, Suidan J, Wasserman J, Antoine C, Young BK. The Apgar score: is it enough? *Obstet Gynecol.* 1985;66:331-336.

35. Goldenberg RL, Huddleston JF, Nelson KG. Apgar scores and umbilical arterial pH in preterm newborn infants. *Am J Obstet Gynecol.* 1984; 149:651-655.

Picture of the Month

Philip R. Cohen, MD, Michael Yunakov, MD (*Contributors*); Murray Feingold, MD (*Section Editor*)

Figure 1.

Figure 2.

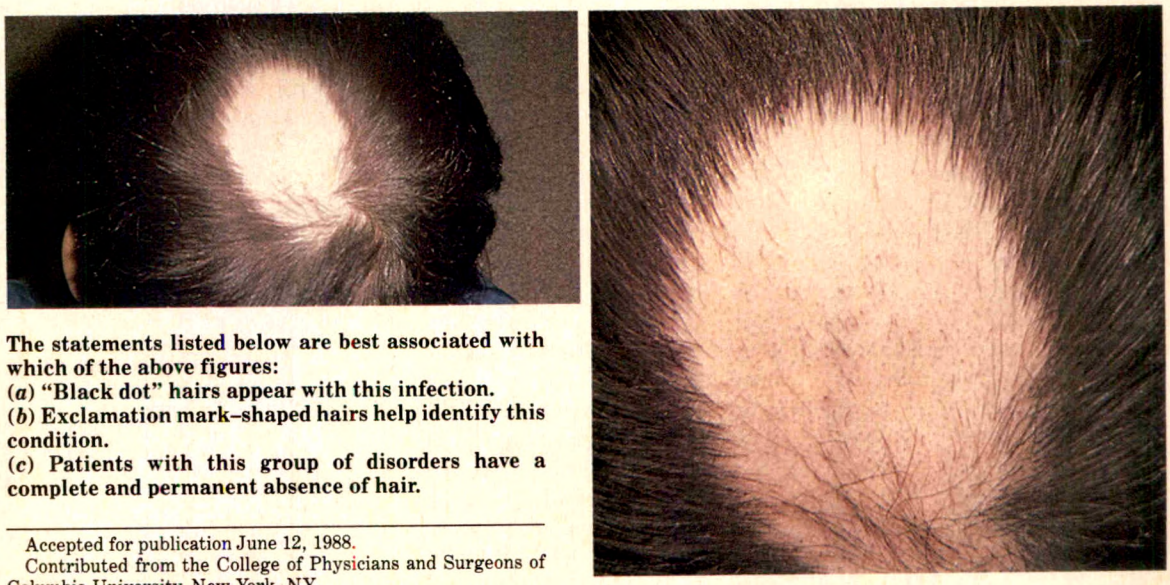


Figure 3.

The statements listed below are best associated with which of the above figures:
(*a*) "Black dot" hairs appear with this infection.
(*b*) Exclamation mark–shaped hairs help identify this condition.
(*c*) Patients with this group of disorders have a complete and permanent absence of hair.

Accepted for publication June 12, 1988.

Contributed from the College of Physicians and Surgeons of Columbia University, New York, NY.

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—A small, single-vertex lesion of scalp aplasia cutis congenita.

Fig 2.—*Trichophyton tonsurans* tinea capitis with resultant alopecia, kerion formation, and postauricular adenopathy.

Fig 3.—A well-circumscribed, oval area of patchy or discoid alopecia areata located on the scalp of a young child.

(*a*) *Trichophyton tonsurans*, an endothrix anthrophilic organism, is currently the most common dermatophyte infection causing tinea capitis in children. Occurring most frequently in black children, and equally distributed between males and females, the clinical manifestations of a *T tonsurans* infection are (1) seborrheic or dandrufflike dermatitis; (2) patchy or diffuse alopecia with or without "black dot" hairs (Fig 2); and/or (3) a kerion (a boggy, tender, edematous mass studded with suppurative, perifollicular pustules and nodules), which may be accompanied by fever, malaise, lymphadenopathy, leukocytosis, and a generalized id reaction or morbilliform rash. The black dot hairs are the remnant hair stubs that have broken off at the level of the scalp. Since *T tonsurans* does not fluoresce under examination with a Wood light, the diagnosis may be suggested by finding arthroconidia within the hair shaft on a 10% potassium hydroxide preparation and confirmed by the characteristic growth of wiry or granular sulfur-yellow, close-knot hyphae, which often have a suedelike consistency, and undulating folding on Sabouraud's agar staining with antibiotic therapy. Both direct contact and fomites have been implicated as sources of this contagious tinea infection. Oral microsize griseofulvin and the adjuvant use of a sporicidal shampoo result in suppression of viable spores within 2 weeks, allowing children to return to school within 7 to 14 days after initiation of this therapy.

(*b*) A common cause of hair loss in children is alopecia areata (AA), a condition whose pathogenesis is probably autoimmune with a possible genetic predisposition (approximately 25% family incidence). Clinical hair-loss patterns in AA include (1) patchy or discoid (Fig 3); (2) marginal or ophiasis (a band of hair at the scalp margin is involved); (3) diffuse (>20% loss of total scalp hair without oval patches); (4) totalis (complete scalp alopecia); and (5) universalis (a generalized form in which all scalp, body, and facial hair are lost). Club-shaped hairs or exclamation mark–shaped hairs represent the loose tapered hair shafts produced by a gentle hair pull from the edge of an alopecia patch. In the active phase of AA, in addition to exclamation mark–shaped hairs, pigmented stubble or broken hairs are frequently visible at the border of the patch. Alopecia areata may be present in association with other autoimmune diseases (especially thyroid related), atopy, and/or Down syndrome. Nail changes (primarily pitting and longitudinal ridging) are present in less than one third of affected individuals. An estimated overall frequency of spontaneous remission in patients with AA is approximately 60% after 1 year. Therapies of choice in children—each with variable success—include none, wig, topical and intralesional corticosteroids, multivitamins or minerals, and topical anthralin with or without UV light. Systemic corticosteroids, allergic contact irritants, phototherapy (psoralens and UV-A), and drugs with immune-modulating properties are other available treatment modalities.

(*c*) Aplasia cutis congenita (ACC) is a heterogeneous group of disorders in which there is either a localized or widespread congenital absence of skin. The most frequent location for solitary lesions of ACC (without associated multiple anomalies) is at, or near, the parietal hair whorl of the scalp. The lesions can be small, large, circular, punched out, round, oval, linear, rhomboid, stellate, ulcerated, membranous, atrophic, or bullous.

The diagnosis of ACC is primarily clinical, and a constant histologic feature is the complete absence of adnexal structures. Skull roentgenograms and cranial computed tomograms (with coronal views) are recommended for infants with scalp ACC, since the calvaria directly beneath the lesion may also be absent in up to 30% of these patients. If the underlying bone is absent and the dura exposed, the risk of complications is increased, and surgical intervention is possibly indicated. If the cutaneous lesion is small and shallow, local wound care with subsequent secondary healing is appropriate therapy. The inheritance pattern of scalp ACC is either autosomal dominant or sporadic. Aplasia cutis congenita has also been associated with other conditions, including limb reduction defects, epidermal nevi, overt and occult embryologic malformations, placental infarcts or fetus papyraceus, epidermolysis bullosa, specific teratogens or intrauterine infections, chromosomal abnormalities, ectodermal dysplasias, and other malformation syndromes.

References

1. Herbert AA, Head ES, MacDonald EM. Tinea capitis caused by *Trichophyton tonsurans*. *Pediatr Dermatol*. 1985;2:219-223.
2. Solomon LM, Rippon JW, Lucky AW, et al. Special symposia: tinea capitis: current concepts. *Pediatr Dermatol*. 1985;2:224-237.
3. Esterly NB, Thiers BH, Bergfeld WF, et al. Alopecia areata symposium. *Pediatr Dermatol*. 1987;4:136-158.
4. Mitchell AJ, Krull EA. Alopecia areata: pathogenesis and treatment. *J Am Acad Dermatol*. 1984;11:763-775.
5. Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol*. 1986;14:646-660.

Radiological Cases of the Month

Eval Barzel, MD, Jack O. Haller, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A 17-year-old girl complained of pain in the right hip one year after renal transplant surgery. She had been given high-dose steroids because of early episodes of acute rejection. Physical examination revealed only slight limitation of motion of the right hip. Laboratory data were unremarkable. Roentgenograms of the right hip were normal. A magnetic resonance scan of the pelvis was performed. Selected T_1- and T_2-weighted coronal images of the pelvis are shown (Figs 1 through 3).

Accepted for publication May 17, 1988.

Contributed from the Department of Radiology, Box 1208, State University of New York Downstate Medical Center, Brooklyn.

Reprint requests to Department of Radiology, Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

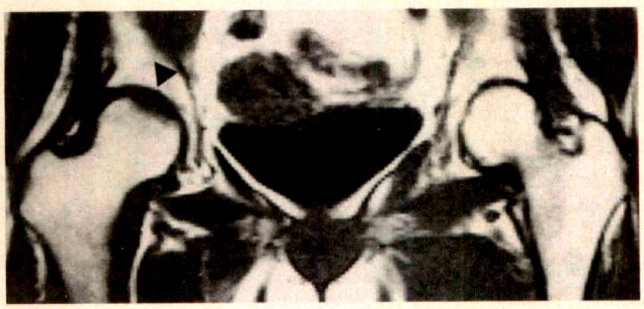


Figure 1.

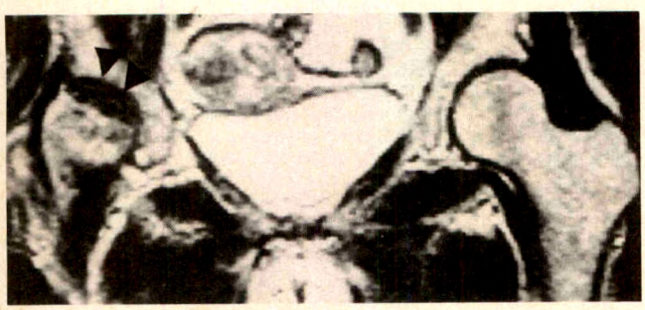


Figure 2.

Figure 3.

Osteonecrosis of the Femoral Head Diagnosed by Magnetic Resonance Imaging

Fig 1.—T_1-weighted coronal magnetic resonance scan of both hips. Both femoral heads are seen. Predominantly white signal marrow is surrounded by black line that represents bone cortex. In superomedial right femoral head, dark area (arrowhead) is seen.

Fig 2.—T_2-weighted coronal magnetic resonance scan of both hips. Bone cortex is black, but normal marrow is mottled gray. Dark area of osteonecrosis (arrowheads) in marrow is seen to better advantage.

Fig 3.—T_1-weighted coronal magnetic resonance scan of both hips. Transplanted kidney (arrowheads) is seen in right hypochondriac area.

Osteonecrosis, also referred to as avascular necrosis and ischemic necrosis of bone, is a complication of steroid use. It results from small blood vessel alteration and infarction of the bone marrow. The infarction may be caused by physical disruption of vessels (from trauma), thrombosis (in sickle cell disease), or vascular compression (from Gaucher's cells in Gaucher's disease). In steroid use and Legg-Calvé-Perthes disease, the exact mechanism of vascular alteration is uncertain. Osteonecrosis most commonly occurs in the femoral head.[1,2]

Children are predisposed to osteonecrosis of the femoral head because the growth plate isolates the blood supply of the metaphysis from the epiphyseal ossification center. In the adult, the perforating metaphyseal vessels enter the femoral head and provide a collateral source of blood flow.[1]

The initiating event may be painful and disabling, as in sickle crisis or trauma, or it may be asymptomatic and unrecognized, as in steroid use or Legg-Calvé-Perthes disease. Once the blood supply is lost, the cellular elements of the marrow die within days. Trabecular bone remains behind and continues to provide support, but without the cellular elements, bone cannot remodel in response to normal stress. During repair, granulation tissue at the edge of the infarction develops, old trabeculae are resorbed, and new bone is laid down. Resorption of bone at the infarct margin makes the damaged femoral head particularly prone to fracture and collapse. The healing process is slow, and the pathologic sequelae may be late. Thus, the patient may present long after the initiating event.[1]

Typically, the patients complain of hip pain, limitation of motion, and limp. Pain may be referred to the knee. Symptoms often develop insidiously over days to months.[3]

In advanced cases of osteonecrosis, a roentgenogram of the hip is diagnostic, showing typical fractures or collapse. In early disease the roentgenogram may be normal. In these instances, if clinical suspicion is strong, complete evaluation requires further imaging.[4]

A bone scan may detect osteonecrosis despite a normal or nonspecific roentgenogram. In early disease, a "cold spot" is seen in the area of infarction because the radiopharmaceutical cannot deposit within an avascular area. In advanced disease, a hot area can be seen in the bone corresponding to deposition of the radiopharmaceutical in the area of repair.[4] Magnetic resonance imaging, with its high resolution and excellent visualization of the bone marrow, is significantly more sensitive and specific than bone scanning in detecting early disease.[5-9] Magnetic resonance imaging may also demonstrate hip effusions, focal accumulations of bone marrow fat, and bone marrow edema, all of which have been theorized to cause compression of blood vessels and subsequent osteonecrosis.[10,11]

Magnetic resonance imaging can demonstrate the extent of early disease in the bone marrow and should improve the clinician's prognostic ability. A classification based on magnetic resonance imaging has already been suggested, and findings on magnetic resonance imaging have altered the therapy in individual cases.[11]

References

1. Sweet DE, Madewell JE: Pathogenesis of osteonecrosis, in Resnick D, Niwayama G (eds): *The Diagnosis of Bone and Joint Disorders.* Philadelphia, WB Saunders Co, 1981, vol 3, pp 2780-2831.
2. Rogers LF: Miscellaneous conditions, in Juhl JH, Crummy AB (eds): *Paul and Juhl's Essentials of Radiologic Imaging,* ed 5. Philadelphia, JB Lippincott, 1987, pp 254-262.
3. Silverman FN (ed): *Caffey's Pediatric X-ray Diagnosis,* ed 8. Chicago, Year Book Medical Publishers Inc, 1985, vol 1, pp 432-439.
4. Weissman BN, Sledge CB: *Orthopedic Radiology.* Philadelphia, WB Saunders Co, 1986, pp 432-439.
5. Totty WG, Murphy WA, Ganz WI, et al: Magnetic resonance imaging of the normal and ischemic femoral head. *AJR* 1984;143:1273-1280.
6. Mitchell MD, Kundel HL, Steinberg ME: Avascular necrosis of the hip: Comparison of MR, CT, and scintigraphy. *AJR* 1986;147:67-71.
7. Markisz JA, Knowles RJR, Altchek DW, et al: Segmental patterns of avascular necrosis of the femoral heads: Early detection with MR imaging. *Radiology* 1987;162:717-720.
8. Beltran J, Herman LJ, Burk JM, et al: Femoral head avascular necrosis: MR imaging with clinical-pathologic and radionuclide correlation. *Radiology* 1988;166:215-220.
9. Mitchell DG, Kressel HY, Arger PH, et al: Avascular necrosis of the femoral head: Morphologic assessment by MR imaging, with CT correlation. *Radiology* 1986;161:739-742.
10. Mitchell DG, Rao VM, Dalinka M, et al: Hematopoietic and fatty bone marrow distribution in the normal and ischemic hip: New observations with 1.5-T MR imaging. *Radiology* 1986;161:199-202.
11. Mitchell DG, Rao VM, Dalinka MK, et al: Femoral head avascular necrosis: Correlation of MR imaging, radiographic staging, radionuclide imaging and clinical findings. *Radiology* 1987;162:709-715.

Swee H. Fang, MBBS, MRCP(UK); R. Ocejo, MD, FRCPC;
Margaret Sin, MBBS, FRCPC; Neil N. Finer, MD, FRCPC (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A 2220-g female infant was born at 35 weeks' gestation to a healthy 28-year-old mother. The pregnancy was uneventful. Membranes were ruptured three hours before spontaneous vertex vaginal delivery, and there was no evidence of fetal distress.

At birth the infant was active, with normal color, but respiratory distress with tracheal tug and strong inspiratory and expiratory efforts with chest retractions developed rapidly. There was no stridor, and no voice was heard when the infant cried.

In view of the severe respiratory distress, with a high partial arterial carbon dioxide tension of 78 mm Hg, intubation was attempted with size 3 and then size 2.5 endotracheal tubes. The vocal cords were visualized, but it was not possible to pass the endotracheal tube beyond the larynx. Gasping respirations developed, and the baby became apneic. Her chest did not expand when positive pressure was applied with a well-fitting mask and anesthetic bag. Arterial blood gas determinations at this time showed a pH of 6.85, carbon dioxide pressure of 112 mm Hg, and oxygen pressure of 411 mm Hg.

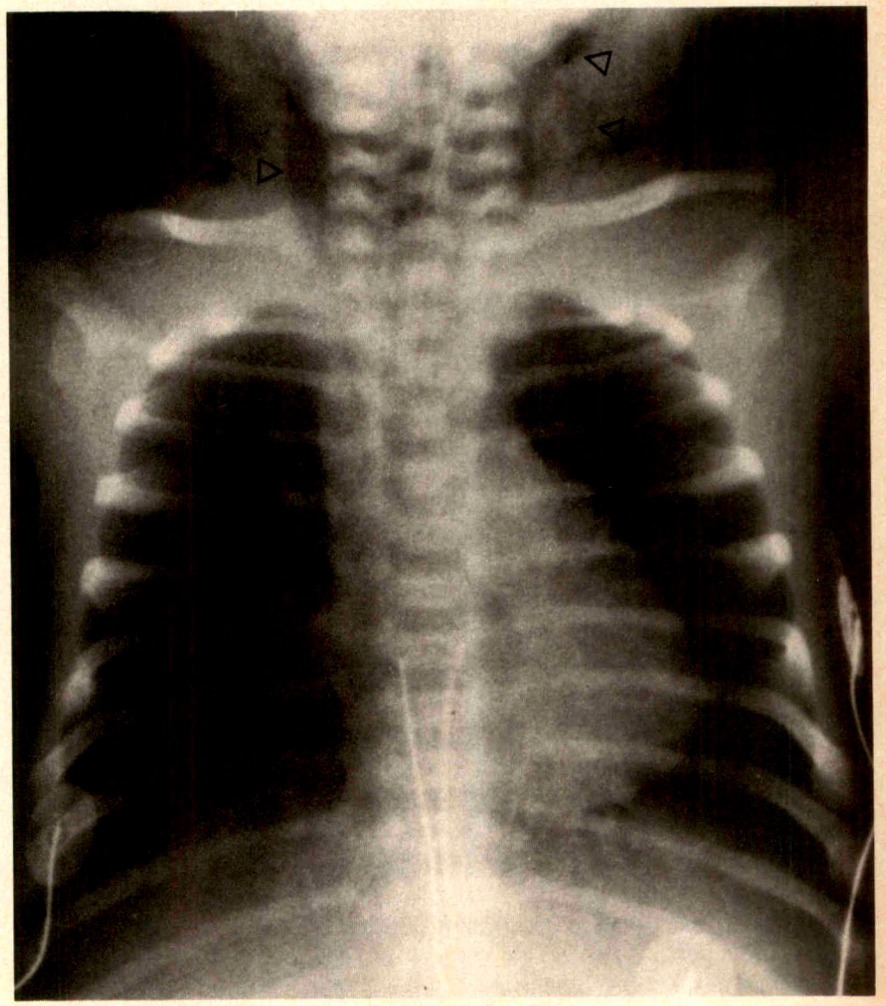


Figure 1.

In view of the patient's rapidly deteriorating condition, a cutaneous transtracheal airway was established. A chest roentgenogram (Fig 1) was done 15 minutes after the procedure. The arterial blood gas determinations at this time showed a pH of 7.12, P_{CO_2} of 42 mm Hg, and P_{O_2} of 211 mm Hg. Circulatory support was provided with fresh-frozen plasma.

Accepted for publication May 17, 1988.

Contributed from the Departments of Newborn Medicine (Drs Fang, Ocejo, and Finer) and Radiology (Dr Sin), Royal Alexandria Hospitals, Edmonton, Alberta.

Reprint requests to Department of Radiology, Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Denouement and Discussion

Congenital Laryngeal Atresia

Fig 1.—Anteroposterior chest roentgenogram shows position of size 16 angiocatheter inserted percutaneously into trachea. Lungs are well expanded, and heart size is normal. Umbilical arterial and venous catheters are seen at level of seventh thoracic vertebra. Subcutaneous air is present in neck (arrowheads).

Fig 2.—Direct sagittal computed tomographic image of larynx and trachea demonstrates solid tissue column (arrow) measuring 1.5 cm at level of larynx, indicating congenital laryngeal atresia.

Emergency percutaneous needle tracheostomy using a size 16 angiocatheter with very high airway pressures of around 60 cm H_2O provided adequate transtracheal ventilation and oxygenation until an emergency tracheostomy was performed. Direct laryngoscopy showed the presence of a fibrous mass at the level of the vocal cords and a minute orifice at the posterior laryngeal inlet. It was not possible to pass even the smallest bronchoscopic telescope beyond the obstruction. As it was possible to position the baby transversely in the computed tomographic scanner, we performed direct sagittal images of the larynx and trachea (Fig 2).

Endoscopy of the esophagus, instillation of methylene blue into the stomach, and a barium esophagram failed to show a tracheoesophageal fistula. Results of neurologic examination were normal, and there were no other abnormalities noted on physical examination or echocardiography. The infant was 4 weeks of age at this writing and was to be sent home with a tracheostomy with plans for definitive surgery at 6 to 12 months of age.

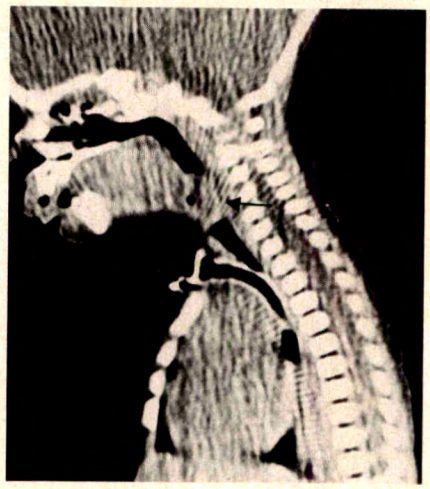


Figure 2.

Congenital laryngeal atresia is a very rare anomaly and was first described by Rossi[1] in 1826. Since then, to our knowledge, 40 cases have been reported. Smith and Bain[2] in 1965 reviewed 26 cases in the world literature and added nine cases of their own. Most of these cases were associated with other potentially fatal congenital abnormalities, and almost all of the reported cases represented studies done at necropsy.[2-5] Paes and colleagues[6] described five infants with rare malformations of the larynx and trachea associated with other congenital abnormalities, with a fatal outcome because of problems of intubation and ventilation. Only four patients with congenital laryngeal atresia have been reported to survive the neonatal period.[7-9]

In 1910, Frazer[10] described the embryonic development of the larynx and theorized that congenital laryngeal atresia was due to the persistence of epithelial fusion of the lateral masses, resulting in the formation of subglottic cartilaginous laryngeal atresia. However, this theory does not explain the development of atresia of the supraglottic part of the larynx, as described by Smith and Bain.[2]

Walander[11] described the embryogenesis of laryngeal development in rats, and this is, in the early stages, applicable to man. During the sixth week of fetal life, the laryngeal lumen is obliterated by proliferative epithe-

lium. This epithelium is resorbed by the tenth week to reestablish the lumen. Failure to do so results in a spectrum of conditions, including narrowing of the lumen, formation of laryngeal web, atresia, and stenosis.

Smith and Bain[2] described three types of congenital laryngeal atresia. In type I the supraglottic and infraglottic portions of the larynx are atretic. In type II the atresia is infraglottic, and in type III the glottic part of the larynx is atretic.

Fox and Cocker[4] divided the cases reported in the world literature into three groups. Group A consisted of cases of congenital laryngeal atresia that occurred with unrelated multiple congenital abnormalities. Group B consisted of cases of congenital laryngeal atresia with associated abnormalities of the esophagus or trachea, such as tracheoesophageal fistula. Group C, of which our infant is an example, consisted of cases in which congenital laryngeal atresia was the only abnormality or was accompanied by a simple cardiac or intestinal anomaly.

Newborns with congenital laryngeal atresia present with severe respiratory distress associated with marked inspiratory and expiratory efforts and chest retraction but without stridor or voice when crying. Complete atresia can occur and, unless treated immediately after birth, is incompatible with extrauterine life. This case illustrates that percutaneous needle tracheostomy and high-pressure transtracheal ventilation is a life-saving procedure that provides adequate ventilation and oxygenation, as shown in animal studies,[12,13] until an emergency tracheostomy can be performed.

Computed tomography has been shown to accurately define the site and extent of narrowed segments of the larynx and trachea.[14]

Reconstructive surgery of the larynx and the return of speech depend on the degree of obstruction. Complete endotracheal tunneling through the atretic area and insertion of a dimethicone or polyethylene stent has been performed, as reported by Cohen.[7] In a case reported by Leibermann and colleagues,[9] the subglottic atresia was removed at the age of 19 months, and reconstruction of the subglottic area was performed with septal cartilage and a T tube. With the advent of new surgical techniques, reconstructive surgery may be successful in maintaining an adequate airway and allowing speech.[15,16]

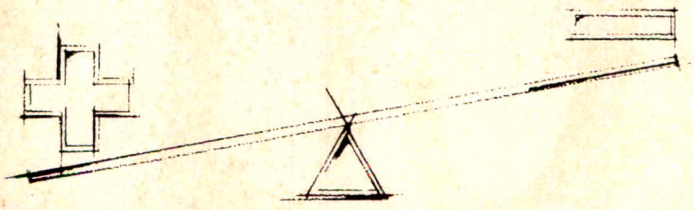
References

1. Rossi F: De nonnullis monstruositatibus in internis humani corporis partibus: Observationes. *Mem R Accad Sci Torino* 1826;30:155.
2. Smith II, Bain AD: Congenital atresia of the larynx. *Ann Otol Rhinol Laryngol* 1965; 74:338-349.
3. Sandison AT: Partial absence of the trachea with live birth. *Arch Dis Child* 1955;30:475-477.
4. Fox H, Cocker J: Laryngeal atresia. *Arch Dis Child* 1964;39:641-645.
5. Woo P, Karmody CS: Congenital laryngeal atresia: Histopathologic study of two cases. *Ann Otol Rhinol Laryngol* 1963;92:391-395.
6. Paes BA, De Sa DJ, Hitch DA: Fatal malformations of the larynx and the upper trachea. *Laryngoscope* 1984;94:1477-1481.
7. Cohen SR: Congenital atresia of the larynx with endolaryngeal surgical correction: A case report. *Laryngoscope* 1971;81:1607-1615.
8. Tucker JD, Tucker G, Vidic B: Clinical correlations of anomalies of the supraglottic larynx with staged sequence of normal human laryngeal development. *Ann Otol Rhinol Laryngol* 1978;87:636-644.
9. Leibermann A, Bar-Ziv J, Karplus M, et al: Subglottic laryngeal atresia associated with tracheoesophageal fistula: Long term survival. *Clin Pediatr* 1985;24:523-525.
10. Frazer JE: The development of the larynx. *J Anat Physiol* 1910;44:156-191.
11. Walander A: The mechanism of origin of congenital malformations of the larynx. *Acta Otolaryngol* 1955;45:426-432.
12. Hughes RK, Davenport C, Williamson H: Needle tracheostomy: Further evaluation. *Arch Surg* 1967;95:295-296.
13. Dobbinson TL, Walen J, Pelton DA, et al: Needle tracheostomy: A laboratory study. *Anaesth Intensive Care* 1980;8:72-80.
14. Liu P, Daneman A: Computed tomography of intrinsic laryngeal and tracheal abnormalities in children. *J Comput Assist Tomogr* 1984;8:662-669.
15. Berkovitz RNP, Bos CE, Pauw KH, et al: Congenital cricoid stenosis, pathogenesis, diagnosis and method of treatment. *J Laryngol* 1978;92:1083-1095.
16. Morimitsu T, Matsumoto I, Okada S, et al: Congenital cricoid stenosis. *Laryngoscope* 1981; 91:1356-1364.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Memorial Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Avenue, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

Risk Management Resources at Your Fingertips

Today, the challenge for physicians and health care institutions to maintain and improve the quality of care is greater than ever. The changing environment of medicine increasingly demands innovative responses from the profession. And, increasingly, physicians and institutions are responding.

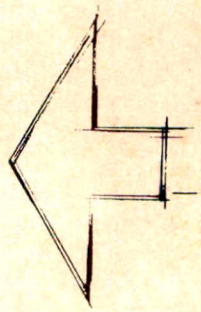


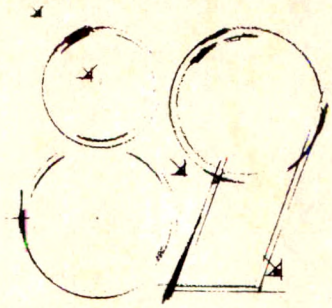
The *Compendium of Patient Safety and Medical Risk Management Programs* is a comprehensive listing of patient safety/risk management resources available from the AMA/Specialty Society Medical Liability Project, the American Medical Association, the Council of Medical Specialty Societies, the Physician Insurers Association of America, national medical specialty organizations and state medical associations.

Featuring Capsule Program Descriptions and Complete Index

This is a one-of-a-kind compilation, a uniquely comprehensive guide to such resources as:

Guidelines and policy statements · Committee and task force activities · Courses and seminars · Self-assessment programs · Data banks · Research projects · Publications, from manuals and books to newsletters and pamphlets · Clearinghouses, resource centers, bibliographies · Videotapes, audiotapes, slide programs





Purchase Includes Periodic Updates

To order, complete the order form below, or for VISA and MasterCard orders call toll-free **1-800-621-8335** (In Illinois, call collect 312-645-4987)

Order Form

YES, please send
The Compendium of Patient Safety and Risk Management Programs, OP140
3-ring binder, approximately 175 pp.

Mail to:
American Medical Association
Book & Pamphlet Fulfillment OP140
P.O. Box 10946
Chicago, Illinois 60610-0946

Name

Institution Group/Company

Address

City State Zip code

Send _____ copies @ $50.00 per copy . . . . . $ _____

Add sales tax in CA, DC, IL and NY . . . . . $ _____

Total amount due . . . . . $ _____

☐ Enclosed is my check in the above total amount due payable to the American Medical Association.

☐ Please charge my ☐ Master Card ☐ VISA

Card Number Expiration date

Cardholder's signature Area code and telephone no.

Published by the American Medical Association

June 1989
Volume 143, Number 6

AJDC

AMERICAN JOURNAL OF DISEASES OF CHILDREN

THE PEDIATRIC FORUM		638
LEADS FROM THE MMWR		645
THE EDITORIAL BOARD SPEAKS . . . : Nightmares on Main Street	*B. D. Schmitt*	649
EDITORIAL: Cleveland, England: Child Abuse in the Public Eye	*V. A. Fulginiti et al*	651
ARTICLES: Acellular Pertussis Vaccine	*T. Aoyama et al*	655
Evaluation of the Vomiting Infant	*L. C. Foley et al*	660
Viral Infections in Cystic Fibrosis	*B. W. Ramsey et al*	662
Pediatric Liver Transplantation	*B. Koneru et al*	669
SPORTS MEDICINE: Oxygen Uptake in Adolescents	*A. C. Hergenroeder*	673
ARTICLES: Metered-Dose Inhaler Use	*G. Benton et al*	678
Lumbar Puncture in Viral Meningitis	*M. Jaffe et al*	682
Vitamin K Absorption and Deficiency	*T. Shinzawa et al*	686
Specialized Camp for Siblings of Children With Cancer	*O. J. Z. Sahler et al*	690
EDUCATIONAL INTERVENTIONS: The Impact of Fever Health Education on Clinic Utilization	*J. S. Robinson et al*	698
ARTICLES: Children With Cataracts	*M. G. Pike et al*	706
Severe Eye Injuries in Children	*P. A. DeRespinis et al*	711
Neurofibromatosis-1 Under 6 Years of Age	*A. C. Obringer et al*	717
Racial Differences in Blood Pressure After Exercise	*F. A. Treiber et al*	720
REVIEW: Toxoplasmosis Needs Evaluation	*M. Koskiniemi et al*	724
ARTICLES: Adolescence: What Is Normal?	*D. Offer et al*	731
Drug Errors in a Neonatal ICU	*M. J. Vincer et al*	737
Bicycle Helmets: Barriers to Use	*J. Howland et al*	741
SPECIAL FEATURES: Radiological Cases of the Month	*R. E. Bokulic et al* *G. S. Crary et al*	747 749

For clean, protected skin

Baby Magic® Baby Bath

- Clinically proven hypo-allergenic[1]
- pH balanced to match babies' skin[1]
- Cleans gently without removing natural skin oils
- Milder than the leading bar soap[1]
- Tear-free

Baby Magic® Baby Lotion

- Clinically proven hypo-allergenic[1]
- pH balanced to match babies' skin[1]
- Special moisturizers leave babies' skin soft
- Helps protect against irritating wetness in the diaper area

1. Data on file, The Mennen Company.

Call 1-800-325-7654 to receive a Baby Magic® clinical overview.

T E S T E D B Y S C I E N C E A N D T I M E

by MENNEN

©1989 The Mennen Co.

AJDC AMERICAN JOURNAL OF DISEASES OF CHILDREN

VOL 143 NO. 6 June 1989

Copyright © 1989 by the American Medical Association

Monthly Circulation >44 500
Also published in French

THE PEDIATRIC FORUM

638 **The Pediatrician as Mother** Lydia Furman, MD, Boston, Mass . . . **Umbilical Cord Circumference at Birth** Daksha Patel, MD; Marcia Dawson, MD; Pattabiraman Kalyanam, MD; Erika Lungus, RN; Howard Weiss, MD; Emalee Flaherty, MD; Ernest G. Nora, Jr, MD, Chicago, Ill . . . **Plasma Support for Surgery in a Premature Infant With Factor IX Deficiency** Charles H. Pegelow, MD; Maria Carmen Borromeo Antigua, MD; Doured Daghastani, MD; Emmalee Setzer Bandstra, MD, Miami, Fla . . . **Congenital Hypothyroidism in Spanish-Surnamed Infants in Southern California: Increased Incidence and Clustering of Occurrence** Robert Penny, MD; Pam Hoffman, RN; Lorayne Barton, MD, Los Angeles, Calif . . . **Comment on 'The Pediatrician as a Consultant'** Richard L. Levenson, Jr, MA, MS, Ed, Ted E. Becker, Jr, MD, New York, NY; Gunmar B. Stickler, MD, Rochester, Minn . . . **Capillary and Venous Bilirubin Values: They Are Different—and How!** Arthur I. Eidelman, MD; Michael S. Schimmel, MD; Nurit Algur, MSc; Uri Eylath, PhD, Jerusalem, Israel . . . **Growth Response of Growth Hormone—Deficient Patients to 0.06 mg/kg Compared With 0.10 mg/kg Three Times per Week of Biosynthetic Growth Hormone** Arlan L. Rosenbloom, MD, Carole L. Knuth, PA-C, Gainesville, Fla . . . **Sunflower Seed Bezoar Presenting as Diarrhea** J. Marshall Dent III, MD, Stanley I. Levine, MD, PhD, Columbus, Ga . . . **Passive Inhalation of Marijuana, Phencyclidine, and Freebase Cocaine ('Crack') by Infants** Richard H. Schwartz, MD, Vienna, Va

645 **LEADS FROM THE MMWR**

THE EDITORIAL BOARD SPEAKS . . .

649 **Nightmares on Main Street**
Barton D. Schmitt, MD, Denver, Colo

EDITORIAL

651 **Cleveland, England**
Vincent A. Fulginiti, MD, New Orleans, La,
Richard D. Krugman, MD, Denver, Colo

ARTICLES

655 **Efficacy and Immunogenicity of Acellular Pertussis Vaccine by Manufacturer and Patient Age**
Tatsuo Aoyama, MD, MPH; Yuji Murase, MD; Makoto Kato, MD; Hideto Iwai, MD; Takashi Iwata, MD, Tokyo, Japan

660 **Evaluation of the Vomiting Infant**
L. Christopher Foley, MD, Denver, Colo; Thomas L. Slovis, MD, Detroit, Mich; John B. Campbell, MD; John D. Strain, MD; Lee A. Harvey, MD; Dennis W. Luckey, PhD, Denver, Colo

662 **The Effect of Respiratory Viral Infections on Patients With Cystic Fibrosis**
Bonnie W. Ramsey, MD; Edmond J. Gore, PhD; Arnold L. Smith, MD; Marion K. Cooney, PhD; Gregory J. Redding, MD; Hjordis Foy, MD, Seattle, Wash

669 **Marked Transient Alkaline Phosphatemia Following Pediatric Liver Transplantation**
Baburao Koneru, MD, Pittsburgh, Pa; Eduardo Carone, MD, São Pãulo, Brazil; J. Jeffrey Malatack, MD, Pittsburgh, Pa; Carlos O. Esquivel, MD, PhD, San Francisco, Calif; Thomas E. Starzl, MD, PhD, Pittsburgh, Pa

Continued on p 630.

EDITORIAL BOARD

Editor
Vincent A. Fulginiti, MD
American Journal of Diseases of Children
Dean's Office
Room 1529
Tulane University School of Medicine
1430 Tulane Avenue
New Orleans, LA 70112
(504) 584-1989

Associate Editors
William W. Waring, MD
New Orleans, La
Thomas G. Storch, MD
New Orleans, La

Book Review Editor
Peggy C. Ferry, MD
Tucson, Ariz

Administrative Assistant
Joann M. Quane
New Orleans, La

Secretary
Laura Martin
Tucson, Ariz

Hugh D. Allen, MD, Columbus, Ohio
Milton I. Arnold, MD, Los Angeles, Calif
Alan D. Bedrick, MD, Tucson, Ariz
Richard W. Blumberg, MD, Atlanta, Ga
Ben H. Brouhard, MD, Cleveland, Ohio
George W. Brown, MD, Los Lunas, NM
James J. Corrigan, Jr, MD, Tucson, Ariz
Beverly B. Dahms, MD, Cleveland, Ohio
Murray Feingold, MD, Boston, Mass
Patricia Ferrieri, MD, Minneapolis, Minn
Laurence Finberg, MD, Brooklyn, NY
Boyd W. Goetzman, MD, PhD, Davis, Calif
John D. Johnson, MD, Albuquerque, NM
James P. Keating, MD, St Louis, Mo
Elizabeth R. McAnarney, MD, Rochester, NY
Henry L. Nadler, MD, Chicago, Ill
Robert Penny, MD, Los Angeles, Calif
Albert W. Pruitt, MD, Augusta, Ga
Barton D. Schmitt, MD, Denver, Colo
E. Richard Stiehm, MD, Los Angeles, Calif
William B. Strong, MD, Augusta, Ga
Beverly P. Wood, MD, Rochester, NY

Continued from p 629.

SPORTS MEDICINE

673 **Predicting Maximum Oxygen Uptake in Adolescents**
Albert C. Hergenroeder, MD, Houston, Tex,
Robert B. Schoene, MD, Seattle, Wash

ARTICLES

678 **Experience With a Metered-Dose Inhaler With a Spacer in the Pediatric Emergency Department**
Grey Benton, RRT, MA; Randolph C. Thomas, MD; Bruce G. Nickerson, MD; John C. McQuitty, MD; Jerry Okikawa, RRT, MBA, Oakland, Calif

682 **The Ameliorating Effect of Lumbar Puncture in Viral Meningitis**
M. Jaffe, MB, BCh, MRCP(Edin), DCH; I. Srugo, MD; E. Tirosh, MD; A. A. Colin, MD; Y. Tal, MD, Haifa, Israel

686 **Vitamin K Absorption Capacity and Its Association With Vitamin K Deficiency**
Takeshi Shinzawa, MD; Tetsuo Mura, MD; Mikio Tsunei, MD; Kazou Shiraki, MD, Yonago, Japan

690 **Evaluation of a Camp Program for Siblings of Children With Cancer**
Olle Jane Z. Sahler, MD, Paul J. Carpenter, PhD, Rochester, NY

EDUCATIONAL INTERVENTIONS

698 **The Impact of Fever Health Education on Clinic Utilization**
J. Stephen Robinson, MD, PhD, MPH; Mei-Ling M. Schwartz, MPH; Katherine S. Magwene, MPH; Saundra A. Krengel, LVN; Diane Tamburello, MPH, Panorama City, Calif

ARTICLES

706 **Neurological and Developmental Findings in Children With Cataracts**
Michael G. Pike, MA, MRCP; James E. Jan, MD, FRCPC; Peter K. H. Wong, MD, FRCPC, Vancouver, Canada

711 **A Survey of Severe Eye Injuries in Children**
Patrick A. DeRespinis, MD; Anthony R. Caputo, MD; Philip M. Fiore, MD; Rudolph S. Wagner, MD, Newark, NJ

717 **The Diagnosis of Neurofibromatosis-1 in the Child Under the Age of 6 Years**
Angela C. Obringer, PhD; Anna T. Meadows, MD; Elaine H. Zackai, MD, Philadelphia, Pa

720 **Racial Differences in Young Children's Blood Pressure**
Frank A. Treiber, PhD; Linda Musante, PhD; William B. Strong, MD; Maurice Levy, EdD, Augusta, Ga

REVIEW

724 **Toxoplasmosis Needs Evaluation**
Marjaleena Koskiniemi, MD, PhD; Maija Lappalainen, MD; Klaus Hedman, MD, PhD, Helsinki, Finland

Continued on p 633.

The AMERICAN JOUR OF DISEASES OF C DREN is a member of the sortium of AMA journals l below. The Archives rea more than 41 500 readers countries each month. complete text of all AMA nals is available on the ME data base from Mead Central, Dayton, Ohio.

JAMA The Journal of the American Medical Association
AJDC American Journal of Diseases of Children
archives of Dermatology
archives of General Psychiatry
archives of Internal Medicine
archives of Neurology
archives of Ophthalmology
archives of Otolaryngology-Head & Neck Surgery
archives of Pathology & Laboratory Medicine
archives of Surgery

James H. Sammons, MD, Executive Vice-P dent

James S. Todd, MD, Senior Deputy Execu Vice-President

Kenneth E. Monroe, Deputy Executive V President

Theodore R. Chilcoat, Jr, Assistant Execu Vice-President

M. Roy Schwarz, MD, Assistant Executive V President

George D. Lundberg, MD, Vice-Presid Scientific Information

John T. Baker, Vice-President, Publishing

Norman D. Richey, Director, Publication Proc tion and Printing Division

Lee A. Parent, Director, Circulation-Fulfillm Division

Dennis Joseph Dennehy, Director, Advertising Sa and Promotion Services Division

Thomas J. Carroll, Director, Department Advertising Communication

Raymond Christian, Director, Advertising S vices Department

When I was a child there was no Orimune®

Poliovirus Vaccine Live Oral Trivalent

Jackie DiLorenzo of Hastings-on-Hudson, New York, contracted polio in 1950, before a vaccine became available. She spent ten years in rehabilitation, during which time she underwent nine operations on her spine, legs and feet. Jackie currently lives in a house adapted for wheelchair living.

Ask your Lederle representativ about the award-winning **Adolescent Wellness Prog**

Lederle Biologicals Protecting Families Through Immunization®

Please see following page for brief summary of prescribing information.

When I was a child there was no Orimune®

Proven in Millions of US Patients

ORIMUNE was the first live, oral, trivalent polio vaccine. No other oral polio vaccine has done more to help eradicate wild poliovirus in the US. Over 500 million doses have been distributed to date.

Proven Safety* Record

Lederle takes every precaution during production and testing to ensure the safety of ORIMUNE. This dedication is evident by our 27-year safety record.

Uninterrupted Supply

Lederle has consistently met the nation's needs for oral polio vaccine for about 27 years. In fact, when all other US manufacturers discontinued the production of oral polio vaccine, Lederle has remained committed to this essential product and to the health of America's children.

Available in Single-Doses

ORIMUNE is available in convenient, unit-dose DISPETTES® to help assure dosage accuracy and avoid the risk of contamination.

*Paralytic disease following ingestion of live poliovirus vaccine has been reported on rare occasions in individuals receiving the vaccine or in their close contacts.

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

A Brief Summary

Please see package insert for full description, directions for use, and references.

INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*
CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live polioviruses that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev. 8/86

orimune®
poliovirus Vaccine Live Oral Trivalent

Lederle Biologicals
Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470
© 1989 Lederle Laboratories
313-9B

PUBLICATION STAFF
Offices: 535 N Dearborn St
Chicago, IL 60610

Managing Editor and Director, AMA Specialty Journals:
Michael D. Springer

Associate Editor:
Julie Foreman

Production Manager:
Marlene M. Hinsch

Assistant Production Managers:
John R. Sayban, Mary C. Steermann

Editorial Processing Manager:
Cheryl Iverson

Assistant Editorial Processing Manager:
Paula Glitman

Permissions and Graphic Design Manager:
Dennis J. Shipley

Staff Assistants:
Diane Darnell
Bonnie Van Cleven

Copy Editing:
Patricia A. Predey (Supervisor)
Vickey Golden (Free-lance Coordinator)
Paul Frank (Senior Copy Editor)
John Radanovich
Philip Rogers
Janice Snider

Production Supervisors:
Betty Frigerio (Advertising)
Thomas J. Handrigan (Illustrations)
JoAnne Weiskopf (Layout)

Proofreading:
Teresa H. Omiotek
Richard T. Porter
Jennifer Reiling
Barbara Wojtowicz

Production Associate:
Susan Price

Art and Senior Production Assistants:
Melinda Arcabos
Cari Biamonte
Laura Bleiler
Karen Branham
Cynthia Gelper
Jerri Hall-Gortowski
Anita Henderson
Debra Lucas
Susan McIlwaine
Juliana K. Mills
Dorothy Patterson
E. Ruth White
Ellen Yoshihara

Production Assistant:
Darlene E. Filips

Editorial Assistant:
Jean Schaffner

Department of Scientific and Socioeconomic Indexing:
Norman Frankel (Director)
George Kruto
Susan McClelland
Mary Kay Tinerella

Please address communications concerning accepted or published communications to AMA Specialty Journals, 535 N Dearborn St, Chicago, IL 60610.

EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

Continued from p 630.

ARTICLES

731 Adolescence
Daniel Offer, MD, Eric Ostrov, JD, PhD, Chicago, Ill;
Kenneth I. Howard, PhD, Evanston, Ill

737 Drug Errors and Incidents in a Neonatal Intensive Care Unit
Michael J. Vincer, MD, FRCPC; Joan M. Murray, RN;
Anne Yuill; Alexander C. Allen, MD, FRCPC;
Jacquelyn R. Evans, MD, FRCPC;
Dora A. Stinson, MD, FRCPC, Halifax, Canada

741 Barriers to Bicycle Helmet Use Among Children
Jonathan Howland, PhD, MPH; James Sargent, MD; Michael Weitzman, MD;
Thomas Mangione, PhD; Robert Ebert, PhD, Boston, Mass;
Marianne Mauceri, RN, New Bedford, Mass; Marie Bond, EdM, Boston, Mass

SPECIAL FEATURES

Radiological Cases of the Month

747 Ronald E. Bokulic, DO; Robert C. Beckerman, MD;
Denise Mulvihill, MD (*Contributors*), New Orleans, La;
Beverly P. Wood, MD (*Section Editor*), Rochester, NY

749 Gretchen S. Crary, MD; Barbara A. Burke, MD; Bennett A. Alford, MD;
René P. du Cret, MD (*Contributors*), Minneapolis, Minn;
Beverly P. Wood, MD (*Section Editor*), Rochester, NY

BOOK REVIEWS

Books Received but Not Reviewed (pp 716, 744)

634 INSTRUCTIONS FOR AUTHORS

654 INDEX TO ADVERTISERS

AJDC, American Journal of Diseases of Children (ISSN 0002-922X) is published monthly by the American Medical Association, 535 N Dearborn St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

SUBSCRIPTION RATES—The subscription rates for the American Journal of Diseases of Children are as follows: $48 for one year, $81 for two years in the United States and US Possessions; all other countries, one year, $58; two years, $101 for surface delivery. (For expedited air delivery to most countries, add $15 surcharge for one year subscription, $30 for two years.) Rates for subscriptions for delivery to Japan or South Korea are available through exclusive agents—contact the publisher. ***Special rates for residents and medical students in the United States and US Possessions are available.*** Address inquiries to the American Medical Association, Circulation and Fulfillment Division, 535 N Dearborn St, Chicago, IL 60610. Phone: (312) 280-7168.

CHANGE OF ADDRESS—POSTMASTER, send all address changes for AJDC, American Journal of Diseases of Children. Attention: Subscription Department, 535 N Dearborn St, Chicago, IL 60610. Notification of address change must be made at least six weeks in advance, include both old and new addresses, a recent mailing label, and your new zip code.

ADVERTISING OFFICES: Eastern: 600 Third Ave, Suite 3700, New York, NY 10016 (**Manager:** Robert C. Corcoran [212-867-6640]; **Representative:** Phillip B. Altamore); **Midwest/Farwest:** 535 N Dearborn St, Chicago, IL 60610 (**Manager:** Thomas J. Carroll [312-280-7182]; **Representative:** John P. Cahill, Midwest/Farwest)

Advertising Principles: Each advertisement in this issue has been reviewed and complies with the principles governing advertising in AMA scientific publications. A copy of these principles is available on request. The appearance of advertising in AMA publications is not an AMA guarantee or endorsement of the product or the claims made for the product by the manufacturer.

Instructions for Authors

NEW MANUSCRIPT PROCEDURE

On Jan 1, 1988, *AJDC* initiated a new procedure. Manuscripts submitted to *AJDC* will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information.—Please send manuscripts and correspondence by first-class mail (*do not use registered, certified, or express mail*) to the Editor, Vincent A. Fulginiti, MD, *AJDC*, Dean's Office, Room 1529, Tulane University, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval *if requested* by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

Step 1.—*Cover Letter.*—All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNATURES):

1. *Copyright Release.*—"In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA."

2. *Statement of Affirmation.*—"This manuscript has not been published anywhere in any language and is not under simultaneous consideration by another publication. This manuscript is original and ALL authors have seen and approve of its contents."

3. *Financial Disclosure.*—List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg, employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of *AJDC*.

Step 2.—*Manuscript Format.*—All articles submitted should have the following features:

1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.

2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. *Do not use justified right margins.*

3. Title should be no more than 75 characters.

4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.

5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.

6. Writing style should conform to proper English usage and syntax; consult the *American Medical Association Manual of Style*, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.

7. Abstract should be limited to 135 words or less.

8. Each table should be typed, with a title, on a separate sheet of paper, with *each line, including headings, double-spaced*. Continuations should be on a second sheet with all headings repeated.

9. Use Système International (SI) measurements throughout the manuscript.

10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed *label* and affixed on the back of each illustration. *Do not write directly on the print.*

Magnification and stain should be provided for histologic sections. Full-color illustrations should be submitted as 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glass-mounted transparencies or color prints. Fee is $400 for up to six square-finished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from *both* parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below.

Journal Articles: Sell EJ, Gaines JA, Gluckman C, Williams E. Persistent fetal circulation: neurodevelopment outcome. *AJDC*. 1985;139:25-28.

Books: Krmpotic-Nemanic J, Kostovis I, Rudan P. Aging changes of the form and infrastructure of the external nose and its importance in rhinoplasty. In: Conly J, Dickinson JT, eds. *Plastic and Reconstructive Surgery of the Face and Neck*. New York, NY: Grune & Stratton; 1972:84-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

Authors are responsible for the accuracy of the references.

12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.

13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from *publisher* and *author*. Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3.—*Special Departments.*—Criteria for several special departments are given below.

1. *The Pediatric Forum.*—This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of *AJDC*. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRIPLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED, SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.

2. *From Research to Relevance.*—PURPOSE: To focus on significant research that has a high probability of being translated into clinical usefulness.

3. *Educational Interventions.*—PURPOSE: To share information concerning any educational efforts in the broad field of pediatrics.

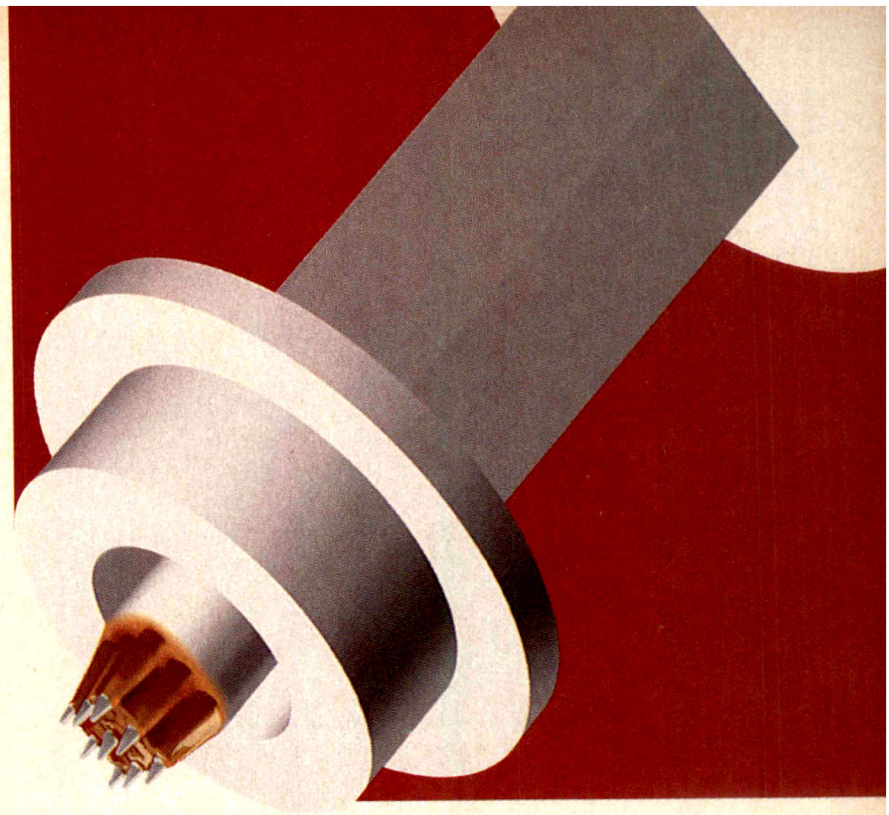
4. *Sports Medicine.*—PURPOSE: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

5. *Picture of the Month.*—Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.

6. *Radiological Case of the Month.*—Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- ____ 1. Cover letter with name, address, and telephone number of corresponding author.
- ____ 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors.
- ____ 3. Original typed manuscript plus three copies.
- ____ 4. Triple-spacing; double-spacing for tables and legends.
- ____ 5. Right margins UNJUSTIFIED.
- ____ 6. Title 75 characters or less.
- ____ 7. Abstract included.
- ____ 8. References in proper format, cited in numerical order.
- ____ 9. Four sets of illustrations.
- ____ 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- ____ 12. Permission forms for illustrations previously published elsewhere.



The symbol of accuracy and clarity in TB screening

Accuracy

98.8% agreement with Mantoux[1]

Co-positivity of MONO-VACC and MANTOUX test[1]

Study	N	Mantoux Positive	MONO-VACC Positive	Positive Agreement
STOCKER	1,406	279	274	**98.2%**
KRAVITZ, et al	1,959	87	87	**100.0%**
BYRD, et al	1,423	256	253	**98.8%**
GRABAU	2,022	60	60	**100.0%**
FREOUR, et al	443	195	188	**96.4%**
FURCOLOW, et al	670	258	254	**98.6%**
JENKINS, et al	84	80	84*	**100.0%**
TOTAL	8,007	1,215	1,200	**98.8%**

Adapted from Federal Register[1]

*Of these 84 bacteriologically-confirmed tuberculin patients, all 84 were correctly identified by MONO-VACC, while only 80 were considered by an FDA review panel to have had a positive reaction to Mantoux. The four "false negative" Mantoux responses (5-9 mm induration) would be considered positive by American Thoracic Society Standards.

†Tine Test and Aplitest are registered trademarks of Lederle Laboratories and Parke-Davis, respectively.

As with all screening tests, positive reactions should be confirmed by a standard Mantoux test.

Please see brief summary of product information on an adjacent page.

A reassuringly low rate of false negatives

A 1.6% incidence of false negatives (a 5.1% incidence of false positives)[2]–reportedly lower than Tine Test®† (O.T.) or Aplitest®† (PPD)[2]

Clarity

A single, easy-to-read reaction

MONO-VACC–the *only liquid* tuberculin screening test–is simple to administer, highly acceptable to patients, *and* easy to interpret.

MONO-VACC® TEST (O.T.) (TUBERCULIN, OLD)

To order MONO-VACC, call toll-free:
1-800-327-2842 Ext 113
(In Florida, call: 1-305-593-9577 Ext 113)

Distributed by
MERIEUX INSTITUTE, INC
Miami, FL 33126

Manufactured by
INSTITUT MÉRIEUX
Lyon–France
US Lic No. 384

© 1989, Merieux Institute, Inc

The symbol of accuracy and clarity in TB screening

MONO-VACC® TEST (O.T.) (TUBERCULIN, OLD)

(TUBERCULIN, OLD)
MONO-VACC® TEST (O.T.)

BRIEF SUMMARY

INDICATIONS
Screening for tuberculosis. Positive reactions should be confirmed by Mantoux method and possibly other diagnostic test procedures.

CONTRAINDICATIONS
None when test is used as directed.

WARNINGS
Although anaphylactic reactions have not been reported with Mono-Vacc, this remote possibility should be considered and epinephrine should be available.

PRECAUTIONS
Do not apply Mono-Vacc to acneiform skin, hairy areas or where there is inadequate subcutaneous tissue. Although repeated testing of uninfected individuals does not sensitize to tuberculin, it may have a "booster" effect in persons with low levels of sensitivity to homologous or heterologous mycobacterial antigens. Testing should be done with caution in persons with active tuberculosis, however, activation of quiescent lesions is rare. Tuberculin color variation may occur between different lots without alteration of potency or stability. Discard each Mono-Vacc test after use. DO NOT REUSE.

Drug Interactions:
The administration of adrenal corticosteroids or immunosupressive drugs may decrease the intensity of or prevent a tuberculin reaction. Tuberculin sensitivity may decrease or disappear temporarily as a result of febrile illness; measles and other exanthemas; live virus vaccination; sarcoidosis and miliary or pulmonary tuberculosis.

Pregnancy Category C. Tuberculin, Old:
Animal reproduction studies have not been conducted with Tuberculin, Old (Mono-Vacc Liquid Tuberculin Test, O.T.). It is also not known whether Tuberculin, Old can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Tuberculin, Old should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS
Vesiculation, ulceration, or necrosis may occur in highly sensitive subjects at the test site. Pain or pruritus at the test site may be relieved by topical glucocorticoid ointment or ice packs.

1/84

REFERENCES
1. Skin test antigens: Proposed implementation of efficacy review. *Federal Register* 1977;42 (September 30): 5207-5209.
2. Donaldson JC, Elliot RC: A study of co-positivity of three multipuncture techniques with intradermal PPD tuberculin. *Am Rev Respir Dis* 1978;118:843-846.

Distributed by
MERIEUX INSTITUTE, INC
Miami, FL 33126

Manufactured by
INSTITUT MÉRIEUX
Lyon-France
US Lic No. 384

Large multispecialty group in the Northern Virginia area needs bilingual pediatrician to replace retiring physician of 40 years.

Send C.V. to Medical Director:

Falls Church Medical Center

6060 Arlington Boulevard

Falls Church, VA 22044

ACADEMIC PEDIATRIC ONCOLOGIST

The Department of Pediatrics, University of New Mexico School of Medicine, is seeking a BC/BE pediatric oncologist to join an active division of pediatric oncology to share clinical, teaching and research responsibilities. Excellent research opportunities for collaboration with our Cancer Center exist. This is a tenure-line position at the assistant/associate professor level.

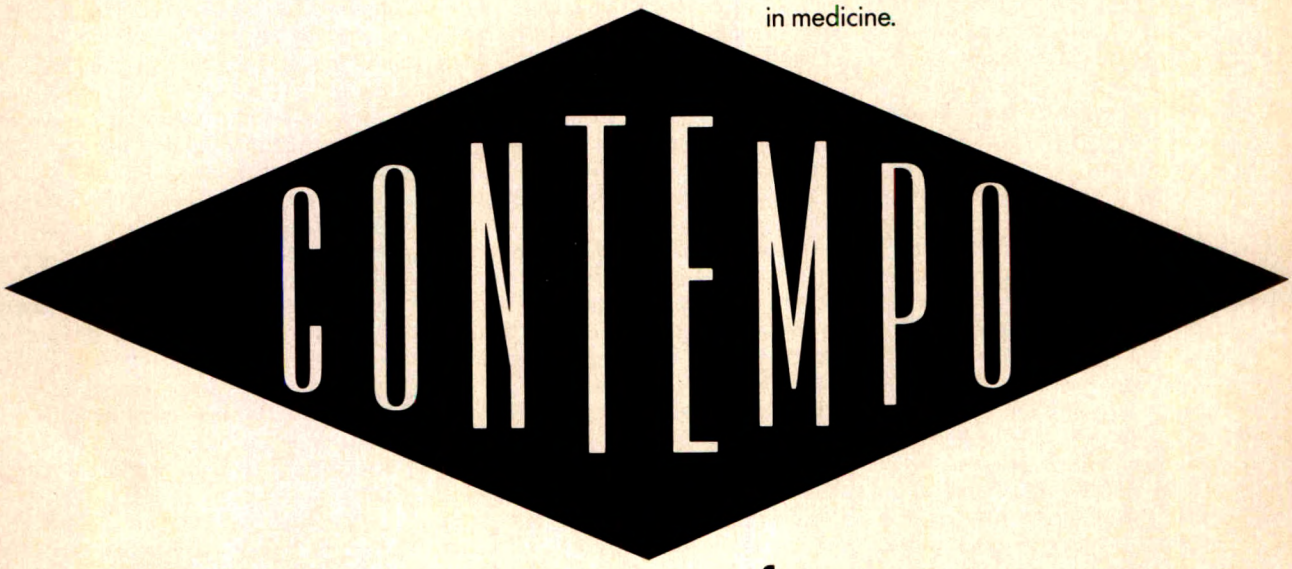
Send letters of inquiry and CV to: John D. Johnson, M.D., Chairman, Pediatrics, University of New Mexico School of Medicine, Albuquerque, NM 87131 (phone 505-277-5551).

CONTEMPO INTERFACE '89

There's nothing like it. Twice a year, the special *Contempo* issue of JAMA comes to life in a six-day program that brings you face-to-face with experts across the medical spectrum.

Interact

Exchange ideas with the authors of *Contempo*, JAMA's survey of the year's key advances in medicine.



interface

Interchange

Catch up on the latest developments in a broad range of specialties.

Interplay

Take back 20 hours of CME credit—and clinical information that will benefit your patients and your practice.

Interested?

Make sure *you're* invited to the next *Contempo Interface*.

Call 1-800-621-8335

(In Illinois call collect, 1-312-645-4987.)

Sponsored by JAMA and the Continuing Medical Education Division of the American Medical Association.

The Pediatric Forum

This department of AJDC *is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.*

The Pediatrician as Mother

Sir:—I am a pediatrician. A brief 9 months ago I had an enlightening experience, which led to a "fellowship" in general pediatrics. I became a mother. This much-undervalued specialty can be as difficult, as stressful, and as utterly enjoyable as the neonatal intensive care unit, the emergency department, the office, or the ward. I do take a break from mothering two short afternoons a week when I "go to work" at a clinic and leave my little one with a housekeeper. I also work at home in the evening after he's asleep. My child eats well, sleeps well, and is growing well. My career is, at best, at a standstill, and our finances are in ruins.

My colleagues are sure I've gone nuts because I decided to raise my child rather than hire someone (like a nanny) for the job. My female colleagues who don't have children sometimes say to me, "Have fun today," as if I were spending the day at an amusement park. My female colleagues with children know better! They all went back to their jobs full time when their children were 8 or 12 weeks old, saying, "I just couldn't stay at home. I'd go crazy." They'd say, "We couldn't afford it," and "I had to get back to my residency." One woman did say to me, "I cried all the way to work each day that first week back and it's still hard to leave in the morning. . . ."

My male colleagues see it differently. One excellent elderly pediatrician said, on learning the number of hours I'm at the clinic, "It must be nice to lead a life of leisure. I wouldn't know about that." What a snub to the mothers of all those clean, loved, and well-fed children he's seen over the years!

A younger colleague compared my search for work at home with the process a doctor goes through recovering from a myocardial infarction or chemical dependency. The analogy may be more insightful than intended. I'm sure that through their experiences those doctors, too, now understand a side of medicine not covered in the standard texts. This colleague then said, "I understand completely your need to work. You're a doctor for God's sake, not a housewife."

This is the way I sometimes feel when I forget that the real work of being at home is raising the child, not cleaning or cooking. And staff from the hospital ask if I could "help out" with attending on the wards. When do I have the time, I wonder—during naps? I savor, though, the wry comment of one graying pediatrician: "Ah, Lydia, I guess you're learning some pediatrics now." I agree.

I now understand the 3-week to 3-month crying in a new way; why it happens, and what to do and not do about it. I don't need to read anything more on breast-feeding. What's hard about nursing, and not written about much, is the rejected, unneeded feeling you have as your healthy baby grows up, weans, and leaves you in the dust. This is an experience avoided and missed by those leaving the baby at age 3 months. What about teething, that diagnosis of last resort for fussy babies? It's real, and it must hurt terribly. I challenge anyone to a 12-hour stint with a teething 5-month-old. And how much worse it is to be the child! Introducing a cup, a spoon and new foods, putting a baby to sleep, introducing a babysitter in a way the baby can understand, teaching a toddler "no," and surviving an entire day with a small child day after day, are not trivial skills, at least to the parents I saw in practice. They say, "You don't know what it's like 'till you have your own." This is true, and you can't know if you're not there.

The profession of pediatrics is dedicated to the health and welfare of children. Mothers are on the front line everyday and deserve respect for their work. Mothering is a valid and challenging job, and women pediatricians with small children need the same support and encouragement to become good mothers as anyone else. I must credit primarily my mother as well as my husband and my pediatrician for helping me.

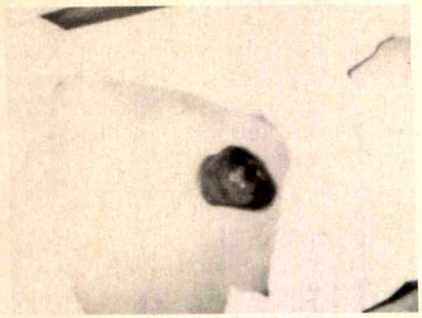
It's unpopular, annoying, and offensive to many to admit that we really don't yet know the long-term (ie, 30 years later) mental health effects of full-time infant day care. Our profession could set an example and make it possible for those women who choose so to stay active in their careers while still being there for their children. Limited scheduled hours, an office at home where feasible, grand rounds at 8 PM (after bedtime) instead of noon (lunchtime), and malpractice fees that are proportional to hours worked would all help.

From the viewpoint of the partners in a practice or the director in a residency program, good help and coverage are hard to find. It's easy to see why most think maternity leave is something to be shortened, not lengthened. But think how much more valuable as a pediatrician the woman will be if she's really "been there" for her kids *and* has retained her skills as a physician. Patients, being mothers themselves, really do understand and accept one's limited availability, provided there is adequate coverage. It's our colleagues we must educate.

LYDIA FURMAN, MD
Department of Adolescent Medicine
Children's Hospital
300 Longwood Ave
Boston, MA 02115

Umbilical Cord Circumference at Birth

Sir:—Recently, we saw a newborn who presented with swelling of the umbilical cord. The cord measured 70 mm



Umbilical cord circumference measured 70 mm at the base of the cord and remained unchanged for the next 2 days.

at its attachment to the umbilicus (Figure). Examination on palpation revealed the presence of crepitus in the cord, and, interestingly, the abdominal roentgenogram revealed loops of bowel herniating through the defect in the umbilicus. The patient was immediately referred to a pediatric surgeon. Subsequently, we became concerned that if the cord had been clamped near the base, it would have resulted in an intestinal obstruction.[1] This episode caused us to examine the following questions: (1) What is the normal size of the neonatal umbilical cord? (2) Do the newborn's measurements and weight have any relationship to the size of the cord at birth?

Review of the literature indicated that much is known about abnormalities of the cord, such as granulomas, infections, and hernias. However, we found no information about the normal cord circumference and the factors that correlate with it.

Patients and Methods.—Between June and September 1986, 191 newborns were enrolled in the study. The umbilical cord circumference at its attachment to the umbilicus was measured on the first day of hospitalization by the senior nurses in the nursery. They also weighed the newborns and obtained chest and abdomen measurements. The mean and SD were calculated for each measurement.

The mean weight, gestational age, chest circumference, and abdominal circumference are given in Table 1. The mean cord circumference of the 191 neonates on admission was 37.6±7.3 mm. For three weight groups, the mean cord circumference differed (Table 2), indicating a progressive rise with increase in weight.

The mean chest circumference was 32.9±2.3 cm (Table 2). The chest circumference was divided into three categories. The mean cord circumference increased with increased chest circumference. The mean abdominal circumference was 30.7±2.8 cm (Table 2). The measurements of the abdominal circumference were divided into three categories. The mean umbilical cord circumferences for those measuring 30 cm, 30 to 31 cm, and 31 cm were 36.3±7.0, 37.9±6.5, and 38.5±7.7 mm, respectively.

Table 1.—Measurements on Neonates and Mean Cord Circumference on Day 1

Measurement (n=191)	Mean±1 SD
Weight	3265.5±537.5 g
Gestational age	39.4±1.5 wk
Chest circumference	32.8±2.3 cm
Abdominal circumference	30.75±2.8 cm
Umbilical cord circumference	37.7±7.3 mm

Table 2.—Mean Cord Circumference for Different Weight, Chest, and Abdominal Categories

Categories*	Mean Cord Circumference, mm (Mean±1 SD)
Birth weight, g	
2500 (13)	35.9±5.0
2501-4000 (164)	37.5±7.4
4000 (14)	40.9±6.4
Chest circumference, cm	
31 (41)	35.1±6.0
31.1-33 (76)	38.3±7.5
33.4 (74)	38.4±7.5
Abdominal circumference, cm	
30 (64)	36.3±7.0
30-31 (41)	37.9±6.5
31 (86)	38.5±7.7

*Numbers in parentheses indicate numbers of patients.

Comment.—Although clamping of the umbilical cord is a routine procedure in delivery rooms throughout the world, umbilical cord circumference is never measured as a routine. Our study indicated that the mean cord circumference at the base where the cord is attached to the umbilicus is 37.7±7.3 mm. Not a single neonate in the study had a cord circumference of 70 mm as seen in our patient. Thus, large circumference must raise suspicion of a hernia. In such a case, either the clamp should be placed away from the base or the clamping should be delayed until the newborn is examined by a physician.

Umbilical cord size varied in our study group depending on the weight of the infant. Neonates weighing less than 2500 g had smaller cords than those weighing more. Umbilical cord circumference was higher for the neonates with larger chest and abdominal circumferences. Five neonates in the study group weighing less than 2500 g were small for gestational age, and all neonates weighing more than 4000 g were large for gestational age, raising an interesting question: What factors regulate the size of the umbilical cord?

The cord usually contains two arteries and one vein surrounded by mucoid connective tissue, often called Wharton's jelly. During the early stage of development, trophoblast at the embryonic pole of the blastocyst attaches to and subsequently invades the endometrium, forming the future umbilical cord.[2] It is conceivable that factors that regulate the growth of the fetus in the uterus influence the size of the umbilical cord.

Daksha Patel, MD
Marcia Dawson, MD
Pattabiraman Kalyanam, MD
Erika Lungus, RN
Howard Weiss, MD
Emalee Flaherty, MD
Ernest G. Nora, Jr, MD
Departments of Pediatrics and Obstetrics
Columbus Hospital
2520 N Lakeview
Chicago, IL 60614

1. Landor JM, Armstrong JM, Dickerson OB, Westerfed RA. Neonatal obstruction of bowel caused by accidental clamping of small omphalocele: report of two cases. *South Med J.* 1963;56:1236.

2. Moore KL. The fetal membranes and placenta. In: *The Developing Human.* Philadelphia, Pa: WB Saunders Co; 1977:101-102.

Plasma Support for Surgery in a Premature Infant With Factor IX Deficiency

Sir.—Surgery for a child with hemophilia B can be safely accomplished by maintaining factor IX levels above 20%.[1] Although this can be done with plasma prothrombin concentrate, its use has been associated with thrombotic complications.[2-5] Fresh-frozen plasma avoids thromboses, but the volumes required are excessive. These potential dangers are magnified in the newborn period, especially in the premature infant.

We report a successful approach to the preoperative and postoperative management of patent ductus arteriosus ligation in an extremely immature infant with documented factor IX deficiency.

Patient Report.—The infant was a 580-g Hispanic male delivered after 24 weeks' gestation complicated only by spontaneous rupture of membranes. The mother was a

23-year-old gravida 7, para 0, aborta 6. Apgar scores were 3, 4, and 7 at 1, 5, and 10 minutes, respectively.

The maternal grandfather has hemophilia B with a factor IX level of 1.8%. He has five affected brothers and two sisters who have hemophilic children. One of his affected brothers has two hemophilic grandsons. The infant's mother was found to have a factor IX level of 23% at the time of genetic counseling.

On the second postnatal day, the infant's factor IX level was found to be 3% while factors II, VII, and X were 40%, 24%, and 34%, respectively. He had received a routine intramuscular vitamin K injection shortly after delivery.

By the third postnatal day, a patent ductus arteriosus was determined to be contributing to his respiratory problems. Indomethacin sodium at a dose of 0.2 mg/kg per day failed to achieve ductus closure. Mild renal insufficiency developed with oliguria and serum creatinine levels increased to 170 μmol/L. Additionally, he developed a pulmonary hemorrhage and prolonged bleeding from puncture sites, presumably due to the combination of patent ductus arteriosus, indomethacin-induced platelet dysfunction, and factor IX deficiency. Fresh-frozen plasma was given to increase his factor IX level to 20% and the bleeding stopped. These problems precluded a second indomethacin course, and it was determined that surgical closure was necessary.

On the 24th day of life, the infant underwent thoracotomy for patent ductus arteriosus ligation. His weight on that day was 510 g. He was given 43 U of human factor IX complex (Bebulin VH, Immuno) prior to the procedure. This dose was contained in a volume of 1 mL. Use of this product was possible with approval of the Federal Food and Drug Administration under the Compassionate Investigational New Drug Exemptions.

The infant's factor IX level before infusion was 5%. At 1, 2½, and 12 hours after the infusion, factor IX levels were 43%, 37%, and 13%, respectively. Factor IX concentrate at the same dosage (43 U) was administered every 12 hours for 5 days, then daily on the sixth and seventh postoperative days. Levels rechecked prior to the 60- and 96-hour infusions were found to be 38% and 46%, respectively. No bleeding or thrombotic problems occurred and no ill effects were attributable to the use of this product.

Echoencephalography performed at 4, 13, and 64 days postnatal age demonstrated only a small left-sided subependymal hemorrhage. The infant was discharged at 126 days weighing 1960 g. As of this writing, he requires oral theophylline and diuretic therapy for a mild degree of bronchial reactivity but is otherwise doing well. No bleeding has been encountered.

Comment.—Prothrombin complex concentrate, which contains factors II, VII, IX, and X, is thought to cause thromboses by virtue of the presence of activated forms of some or all of those factors.[6,7] Alternatively, thrombosis might occur if procoagulant levels are increased disproportionate to those of the naturally occurring anticoagulants, upsetting the balance between them.[8] Since the levels of natural anticoagulants are low in infants,[9,10] it has been recommended that fresh-frozen plasma be used in the newborn period whenever possible.[11]

These concerns prompted the use of continuous infusions of fresh-frozen plasma and multiple-exchange transfusions to manage an intracerebral hematoma in a 5-week-old infant.[12] Hemostasis was successfully maintained, but the therapy was complicated by volume overload and hyperproteinemia.

In this case, the potential adverse effects of volume overload precluded the use of fresh-frozen plasma. Subsequently, an investigational new drug exemption was obtained permitting the use of a product being proposed for Federal Food and Drug Administration approval. This material is said to have minimal amounts of factor VII and no activated factors. No thrombotic complications have been reported in Europe where it is presently licensed.

The replacement dose of factor IX was calculated to avoid excessively high levels of the factors contained in the product. Infusions were calculated to result in nadir levels of approximately 20% and peak levels of 60% to 80%. The initial dose of 43 U was calculated to provide a 55% factor IX increase based on an estimated plasma volume of 6 mL/100 g of body weight and the manufacturer's estimate of a 40% yield of factor IX. Extrapolation of the values obtained at 1, 2½, and 12 hours indicates that the level obtained was 45%, an increment of only 40% and a yield of 28%.

Clearly, the usual formula for calculating the dose of factor IX, 1 U/kg to give a rise of 1.5%,[13] or that proposed by the manufacturer for this product, 1 U/kg to achieve an increase of 1%, are inappropriate for premature infants in view of their relatively large blood volumes.

This experience demonstrates that adequate hemostasis without complicating thrombosis can be provided in a premature infant by the use of human factor IX complex. It is unclear whether the successful outcome was the result of the specific attributes of the product or the avoidance of excessive procoagulant levels. Such therapy must be undertaken with extreme caution due to the grave potential for thrombotic events.

CHARLES H. PEGELOW, MD
MARIA CARMEN BORROMEO ANTIGUA, MD
DOURED DAGHASTANI, MD
EMMALEE SETZER BANDSTRA, MD
Department of Pediatrics R-31
University of Miami
PO Box 016960
Miami, FL 33101-5406

1. Levine PH. The clinical manifestations and therapy of hemophilia A and B. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. *Hemostatis and Thrombosis.* Philadelphia, Pa: JP Lippincott; 1982:86.

2. Kasper CK. Thromboembolic complications. *Thromb Diasth Haemorrh.* 1975;33:640-644.

3. Gruppo RA, Bove KE, Donaldson VH. Fatal myocardial necrosis associated with prothrombin complex concentrate therapy in hemophilia A. *N Engl J Med.* 1983;309:242-243.

4. Agarwal DL, Zelkowitz L, Hletko P. Acute myocardial infarction in a young hemophiliac patient during therapy with factor IX concentrate and epsilon aminocaproic acid. *J Pediatr.* 1981;98:931-933.

5. Feurth JH, Mahrer P. Myocardial infarction after factor IX therapy. *JAMA.* 1981;245:1455-1456.

6. Ratnoff OD. Prothrombin complex preparations: a cautionary note. *Ann Intern Med.* 1974;81:852-853.

7. Hutlin MB. Studies of factor IX concentrate therapy in hemophilia. *Blood.* 1983;62:677-684.

8. Reeve EB. Steady state relations between factor X, Xa, II, IIa, antithrombin III and alpha 2 macroglobulin in thrombosis. *Thromb Res.* 1980;18:19-31.

9. Barnard DR. Inherited bleeding disorders in the newborn infant. *Clin Perinatol.* 1984;11:309-337.

10. Nardi M, Karpatkin M. Prothrombin and protein C in early childhood. *J Pediatr.* 1986;109:843-845.

11. Lusher J. Diseases of coagulation: the fluid phase. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Children.* 3rd ed. Philadelphia, Pa: WB Saunders Co; 1987:1302.

12. Striegel JE, Edson JR. Treatment of a spontaneous intracerebral hematoma with exchange transfusion in an infant with hemophilia B. *J Pediatr.* 1984;105:278-280.

13. Hilgartner MW. Factor replacement therapy. In: Hilgartner MW, ed. *Hemophilia in the Child and Adult.* New York, NY: Masson Publishers USA Inc; 1982:69.

Congenital Hypothyroidism in Spanish-Surnamed Infants in Southern California: Increased Incidence and Clustering of Occurrence

Sir.—From January 1, 1981, through December 31, 1987, 113 358 newborns were screened for congenital hypothyroidism at the Los Angeles County–University of Southern California

Medical Center. Of these newborns, 107 676 had a Spanish surname. The diagnosis of primary congenital hypothyroidism was confirmed in 55 infants with a Spanish surname. Forty-eight of these infants were born without a thyroid gland, 3 had dysgenesis of the thyroid gland, 3 had an inborn error of thyroid metabolism, and 1 had transient hypothyroidism. Thus, the incidence of permanent idiopathic congenital hypothyroidism (12 males and 39 females per 107 676 newborns) in Spanish-surnamed infants is 1 per 2111, confirming findings from a preliminary report from this medical center.[1] This incidence is greater than the 1 per 32 377 for the black population[2] and the 1 per 4254 for the white population.[3]

Additionally, of the 51 newborns, 24 (6 males and 18 females) with permanent idiopathic congenital hypothyroidism were identified over 21 months composed of April, May, and July, throughout the 7 years of screening; the mean (±SD) number of newborns per month was 1.14±0.79. During this 21-month period, 25 509 newborns with a Spanish surname (1262±120 newborns per month) were screened. During the remaining 63 months, 82 167 newborns with a Spanish surname were screened (1288±126 newborns per month), with 27 (0.43±0.59 newborns per month) infants being identified as having permanent idiopathic congenital hypothyroidism. The mean number of newborns screened per month during the two periods did not differ significantly ($P>.2$). In contrast, the mean number of newborns per month identified as having permanent idiopathic congenital hypothyroidism was significantly greater ($P<.005$) during the 21-month period compared with the 63-month period.

The mechanism(s) for the increased incidence or the apparent clustering of the occurrence of permanent idiopathic congenital hypothyroidism is unknown. However, the observations suggest the possibility of both hereditary and environmental influences.

ROBERT PENNY, MD
PAM HOFFMAN, RN
LORAYNE BARTON, MD
Division of Pediatric Endocrinology
Pediatric Pavilion, 4 E8
Los Angeles County–USC Medical Center
1129 N State St
Los Angeles, CA 90033

1. Frasier SD, Penny R, Snyder R. Primary congenital hypothyroidism in Spanish-surnamed infants in Southern California. *J Pediatr.* 1982; 101:315.
2. Brown AL, Fernhoff PM, Milner J, McEwen C, Elsas LS. Racial differences in the incidence of congenital hypothyroidism. *J Pediatr.* 1981; 99:934-936.
3. Fisher DA, Dussault JH, Foley TP, et al. Screening for congenital hypothyroidism: results of screening one million North American infants. *J Pediatr.* 1979;94:700-705.

Comment on 'The Pediatrician as a Consultant'

Sir.—We read with interest Stickler's article "The Pediatrician as a Consultant."[1] Stickler's primary contention is that pediatricians should be able to deal effectively with a broad range of childhood diseases and/or symptoms without referral to specialists. He presents a comprehensive and exhaustive list of typical conditions for which "children do not necessarily need to see specialists," including behavioral disorders, hematologic disorders, disorders of the skin, central nervous system, ear, nose, and throat, heart, gastrointestinal tract, genitourinary tract, musculoskeletal system, and endocrine system, as well as allergies and parasitic infestations.

Stickler is generally correct in his belief that most medical conditions may be treated effectively by the pediatrician, but errs when he does not allow for situations in which referral to psychological and/or psychiatric personnel, for example, are always warranted. We believe that pediatricians in general practice may treat patients with many of the disorders outlined by Stickler. We know, however, that their training in and exposure to some of the behavioral and neurologic disorders listed by Stickler are often incomplete and lead to misdiagnosis.

Attention-deficit hyperactivity disorder (ADHD) is a case in point. It has been our experience, with fourth-year pediatric residents at Columbia College of Physicians and Surgeons and at St Luke's/Roosevelt Hospital, New York, NY, that the diagnosis of ADHD often is not made because "the child was not hyperactive upon examination." This result is not uncommon in children with ADHD, who become very active in group and school settings but function appropriately in a one-on-one situation. As a consultant, the pediatrician who suspects ADHD will need to assess the child in more than just the medical setting. It is not enough to interview parents; consultations with teachers and school psychologists are needed. The pediatrician must glean information from these sources through telephone consultations and by the administration of various child behavior checklists, and then decide on a course of treatment. Especially with ADHD, it is most appropriate for the pediatrician to act as a "consultee" and then use the collected information as a consultant to treat the patient rather than just refer to a specialist. Vital information is lost and the diagnosis may be missed if the pediatrician functions in isolation.

Many of the conditions reported by Stickler may not require referral to specialists. Stickler, however, should have made the point that many of these conditions (eg, school phobia, mild depression, enuresis, encopresis, and asthma) certainly may require concomitant psychotherapeutic treatment. Specific symptoms and conditions such as these should alert the pediatrician to a possible psychogenic cause, and, as a consultant, the physician should consult the *Diagnostic and Statistical Manual of Mental Disorders*,[2] and then perhaps a child psychologist or psychiatrist. In addition, childhood depression and adjustment disorders (adjustment reactions)[2] are best treated by those who have specialized training in individual and family psychotherapy. Dyslexia, which cannot be definitively diagnosed or treated definitively by pediatricians, is similar in that its diagnosis is dependent on psychoeducational evaluations, and its remediation is accomplished by learning specialists. As for behavioral disorders, it is in the best interests of the patient to be referred to a practitioner who has seen many cases, uses the pharmacologic agents daily, and has specialized training in treatment.

There is an implicit economic incentive that may influence pediatricians to treat disorders best handled by specialists. Nevertheless, we applaud Stickler's efforts to train pediatricians as consultants. It is important to add that the art of being a consultant includes an understanding of a child's world, which consists of many settings. When central nervous system and/or psychological disturbance are suspected, the pediatrician must investigate carefully and follow up on the child's behavior in each setting before arriving at a firm diagnosis and

treatment plan. In this way, pediatricians acting as consultants increase their value to and effectiveness for the children whom they treat.

RICHARD L. LEVENSON, JR, MA, MS, ED
Clinical Psychology Intern
Department of Child and Adolescent Psychiatry
St Luke's/Roosevelt Hospital
Doctoral Candidate in School of Community Psychology
Pace University
Department of Psychology
New York, NY

TED E. BECKER, JR, MD
Associate Director
Department of Child and Adolescent Psychiatry
St Luke's/Roosevelt Hospital
St Luke's Site
411 W 114th St
New York, NY 10025

1. Stickler GB. The pediatrician as a consultant. *AJDC*. 1989;143:73-74.
2. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders*. Revised 3rd ed. Washington, DC: American Psychiatric Association; 1987.

In Reply.—The comments by Levenson and Becker are appreciated. However, these comments are precisely the reason we do recommend that pediatricians become more aware of behavior problems. In the past it was mandatory that every pediatrician have some formal training in child psychiatry, but this is no longer routine. I do feel that in the area of attention-deficit disorders, the pediatrician should, indeed, be the first one to review the situation and refer the patient only if this is requested by the parents or if the physician cannot adequately take care of such patients. The fact that 6% of schoolchildren in Baltimore, Md, are being treated with methylphenidate is precisely one of the reasons why there has to be some sanity in dealing with patients who have an attention-deficit disorder. The situation in patients with enuresis is even more critical. As far as I am concerned, every pediatrician has to be able to deal with the problem of enuresis. As I pointed out in my article, adequate training in these areas is mandatory or pediatricians will lose their ability to be consultants.

GUNMAR B. STICKLER, MD
Department of Pediatrics
Mayo Clinic
Rochester, MN 55905

Capillary and Venous Bilirubin Values: They Are Different—and How!

Sir.—Leslie et al[1] recently reported clinically significant differences between capillary and venous bilirubin values. We, too, have compared such paired samples[2] and have also found significant differences, albeit in exactly the opposite direction, ie, higher values in capillary blood as opposed to the finding of Leslie et al that capillary blood levels underestimate venous levels. As our study differed as to both patient population and methodology, we wish to add our comments.

In contrast to the study by Leslie et al, our study was limited only to clinically icteric infants who did not receive phototherapy. Simultaneously drawn paired samples of capillary and venous blood were obtained in random order from 20 infants and analyzed blindly by the Astra-8 (Beckman Instrument Corp Inc, Brea, Calif) autoanalyzer. The mean bilirubin level of the total capillary group was not significantly different than the mean of the venous sample group: 266 μmol/L (range, 222 to 332 μmol/L) compared with 252 μmol/L (range, 212 to 330 μmol/L). However, when paired samples were analyzed, 17 (85%) of 20 of the capillary samples were higher ($P<.01$). Additionally, in six of these 17 samples the difference was of potential clinical significance as defined by Leslie et al, ie, greater than 17 μmol/L.

The striking difference between our results and those of Leslie et al most likely can be explained by differences in methodology. Leslie and coworkers measured bilirubin optically by the direct spectrophotometric method (American Optical bilirubinometer, Buffalo). This technique optically corrects only for oxyhemoglobin but not for other pigments or turbidity. We measured bilirubin directly and chemically by the Jendrassik and Grof modification of the Evelyn and Malloy diazo reaction. The chromophore produced by this technique is a result of the reaction with caffeine diazosulfanilic acid and is measured as a two-point reaction. The first point is an immediate zero-time sample reaction blank and the second point, at 28 s, measures the color change at the peak of the reaction. Thus, there is an automatic correction for all types of pigments and turbidity.[3,4] In addition, the attempt of Leslie et al to explain their results by arguing that environmental light causes photoisomerization in the superficial capillary level is weakened by the fact that a greater difference between capillary and venous blood was found in infants not subjected to phototherapy.

Our findings of elevated capillary levels in icteric infants may be explained by the admixture of tissue bilirubin in capillary samples compared with free-flowing venous blood. In addition, capillary blood is usually drawn from areas of relative stasis and may thus reflect a higher protein level in such capillary blood.

In summary, we agree with Leslie et al who state that "irrespective of the reason of our findings" the results may be clinically significant. Paradoxically, despite the fact that our results are completely opposite from those of Leslie and colleagues, we do agree that venous samples are the more appropriate guide to therapeutic decisions. Further studies are clearly needed, however, to ascertain the relationship of sample site and laboratory technique.

ARTHUR I. EIDELMAN, MD
MICHAEL S. SCHIMMEL, MD
Department of Neonatology
NURIT ALGUR, MSC
URI EYLATH, PHD
Department of Biochemistry Laboratory
Shaare Zedek Medical Center
PO Box 3235
Jerusalem, Israel 91031

1. Leslie GI, Phillips JB, Cassady G: Capillary and venous bilirubin values: Are they really different? *AJDC* 1987;141:1199-1200.
2. Schimmel MS, Algur N, Eidelman AI, et al: Capillary versus venous serum bilirubin measurements: A comparative study, (Hebrew). *Harefuah* 1985;109:387.
3. *Astra-8 Manual*, Brea, Calif, Beckman Instrument Corp Inc, 1981.
4. Sherwin JE, Obernolte R: Bilirubin, in Pierce AJ, Kaplann LA (eds): *Methods in Clinical Chemistry*. St Louis, CV Mosby Co, 1987, pp 1105-1109.

Growth Response of Growth Hormone–Deficient Patients to 0.06 mg/kg Compared With 0.10 mg/kg Three Times per Week of Biosynthetic Growth Hormone

Sir.—The optimal dosage of growth hormone (GH) for the treatment of GH deficiency has not been determined. As little as 2.5 U given once weekly can result in catch-up growth.[1] Raben[2] established a dosage of 2 U three times per week regardless of body size as the standard that was used into the 1980s. In a series of

Mean Growth Velocity of Growth Hormone–Deficient Patients During the First Year of Treatment

Dosage	No. of Patients	Mean ± SD		
		Untreated Growth Velocity	Treated Growth Velocity	Chronologic Age, y
Low dosage (0.06 mg/kg 3 times per wk)	26	3.6 ± 1.3	9.3 ± 1.8*	8.5 ± 3.8
High dosage (0.10 mg/kg 3 times per wk)	116	3.7 ± 1.4	10.3 ± 2.6*	7.8 ± 3.6

*$P<.05$.

reports, the US Collaborative Study Group concluded that a dosage of 0.06 U/kg of body weight three times per week was appropriate. These and other studies were summarized by Frasier[3] in a comprehensive review. He developed a log-dose response curve, based on the published data, that had a very shallow slope, indicating a decreasing cost benefit of increasing dosage.

The purpose of this study was to compare what had been a relatively high dosage of pituitary extract GH (0.12 U or 0.06 mg/kg three times per week) recommended by one manufacturer with the higher dosage (0.2 U or 0.1 mg/kg three times per week) recommended by the other manufacturer of US-distributed GH. The cost of approximately $50 per milligram, rather than safety considerations, makes this determination important.

Methods.—We analyzed first-year treatment data for 26 patients with proven GH deficiency (peak GH response to two to three provocative tests of <10 ng/mL of serum and growth velocity <10th percentile for developmental age), who were receiving 0.06 mg/kg of body weight three times per week by intramuscular or, in a few cases, subcutaneous injection.

Pretreatment growth velocities were derived from at least 6 months of measurements, obtained with a wall-mounted device. Evaluation was done quarterly during GH treatment and included thyroid function studies. Of the 18 patients who were not already being treated for thyrotropin deficiency, 5 were started on thyroid hormone–replacement therapy during the year because of abnormal serum thyroxine values developing with GH treatment.

Data from the Genentech Cooperative Group were obtained in a June 29, 1988 letter from Peter Compton, MA. Comparisons were made using the Student *t* test.

Results and Conclusions.—The first-year growth velocities with GH treatment are shown in the Table along with pretreatment growth velocities for patients receiving the lower dosage and higher dosage of GH. The groups did not differ in pretreatment growth velocities or in chronologic age at the start of treatment.

All patients receiving the lower dosage grew at least 3.3 cm/y faster than they did before treatment. The mean growth velocity in those treated with the lower dosage was 1 cm less per year than in those treated with the higher dosage. The difference from pretreatment velocity with the higher dosage was 115% of that for the lower dosage at approximately 170% of the cost. Obversely, the lower dosage was 86% as effective as the higher dosage at 60% of the cost.

Daily injection of the same total weekly dosage of GH has been noted to be more effective in previously treated patients,[4] suggesting that the optimal cost-effective regimen for treating GH-deficient patients would be the daily administration of one seventh the lower total weekly dosage used in this study (0.025 mg/kg per day).

ARLAN L. ROSENBLOOM, MD
CAROLE L. KNUTH, PA-C
Department of Pediatrics
University of Florida
College of Medicine
PO Box J-296
J. Hillis Miller Health Center
Gainesville, FL 32610

1. Rosenbloom AL. Growth hormone replacement therapy. *JAMA*. 1966;198:364-368.
2. Raben MS. Growth hormone. *N Engl J Med*. 1962;266:82-86, 231-235.
3. Frasier SD. Human pituitary growth hormone (hGH) therapy in growth hormone deficiency. *Endocr Rev*. 1983;4:155-170.
4. Rosenbloom AL, Knuth C, Shulman D. Optimal dosage interval for biosynthetic GH replacement (Somatrem) in GH deficiency. *Pediatr Res*. 1988;23:285. Abstract.

Sunflower Seed Bezoar Presenting as Diarrhea

Sir.—Few objects in medicine are the subject of more bizarre and mythical tales than the bezoar. A bezoar is defined as food or foreign material that has undergone digestive changes in the gut. The translation of this term is "antipoison" or antidote, and the bezoar has been highly praised for its alleged magical and medicinal properties.[1] Bezoars have been used to treat old age, plagues, snake bites, and evil spirits.[2] Queen Elizabeth deemed them precious enough to have had a gold-framed bezoar included in her crown jewels in 1622.[1]

In addition to being medical curiosities, bezoars have been known to cause serious health problems, including upper gastrointestinal tract ulceration and small-bowel obstruction. Bezoars are usually classified into two major groups: trichobezoars, derived from hair, and phytobezoars, derived from plant material. A third group consists of miscellaneous materials of fungal, chemical, or foreign-body origin.[1]

Patient Report.—A 4-year-old black boy presented to the emergency department with symptoms of watery stools, decreased appetite, and abdominal pains. His mother stated that the symptoms began the previous day with watery, dark-green diarrhea, without blood or mucus. His intake since then consisted of sips of apple juice. His temperature was 38°C and he experienced general malaise. There was no vomiting, nausea, or other constitutional symptoms prior to presentation. No medication was given at home. The child's medical history was unremarkable.

The physical examination revealed a temperature of 38.1°C and normal vital signs. It was unremarkable except for a soft, nontender abdomen, with no rebound or guarding. The abdomen demonstrated slightly hyperactive bowel sounds. There was a 2-cm freely movable tubular mass palpable left of the umbilicus that was believed to be consistent with stool.

The rectal examination revealed no palpable mass and resulted in foul-smelling liquid stools without blood or mucus. To conduct studies to rule out a bacterial cause, the child was admitted to the pediatric department with a diagnosis of probable viral gastroenteritis, complicated by mild dehydration.

Admission Studies.—The hemogram revealed a hemoglobin level of 136 g/L, a hematocrit value of 0.40, and a white blood cell count of 9.2×10^9/L, with 0.76 granulocytes. The serum electrolyte levels were as follows: sodium, 139 mmol/L; potassium, 3.9 mmol/L; chloride, 99 mmol/L; and carbon dioxide, 26 mmol/L. The serum urea nitrogen level was 2.1 mmol/L, the glucose level was 5.1 mmol/L, and the creatinine level was 53.04 μmol/L. The child's urinalysis revealed 2+ ketones but otherwise

normal results. A flat-plate roentgenogram of the abdomen showed no definite soft-tissue mass, and, except for a large amount of fecal material in the sigmoid colon and rectum, was normal.

Hospital Course.—On the first day of hospitalization, the child had 12 foul-smelling watery stools and maintained a low-grade fever up to 38.3°C. Stool studies showed no white blood cells. The results of rotavirus testing were negative. Gram's stains of the stool revealed a moderate number of gram-positive and gram-negative cocci as well as gram-negative rods. The possibility of *Salmonella* enteritis was considered, and culture specimens of the stool were obtained.

The following day the child's diarrhea persisted, with 11 additional stools. On day 3, the child began passing what appeared to be seeds. That evening, on reexamination, he was noted to have a large impaction consisting of a bezoar of sunflower seeds. Several attempts to remove this bezoar manually, with glycerin and bisacodyl (Dulcolax) suppositories, were unsuccessful. The child had an additional 16 stools on this day. Twenty-four hours later, following several unsuccessful attempts to remove the bezoar, we agreed that manual removal would require general anesthesia. This proceeded without complications, and a hard mass of sunflower seeds was removed from the child's rectum. The child did well following this procedure, with total resolution of his diarrhea. He was discharged on day 5 without sequelae.

The results of a follow-up barium enema given several months after discharge were normal. There was no evidence of any preexisting constriction that might have predisposed the boy to the formation of this bezoar.

Comment.—We have found only one report of a sunflower bezoar in the literature. That patient presented with extreme constipation rather than diarrhea.[3] Our case is unusual because the child presented with signs and symptoms highly suggestive of bacterial enteritis. This impression was supported by the sudden onset, elevated temperature, Gram's-stain findings, and profuse nature of the diarrhea. Most bezoars develop gradually and, unless obstruction occurs, rarely result in difficulties for the patient. When obstruction does occur, symptoms of nausea, vomiting, and abdominal pain predominate, rather than diarrhea. Apparently, there was insufficient time for this sunflower seed bezoar to become large enough to bring about a total obstruction. The partial obstruction that did occur resulted in the profuse, watery diarrhea that brought the child to medical attention. The admitting history did not elicit information suggesting an abnormal dietary intake. Subsequent to the diagnosis, follow-up questioning confirmed that the child had access to and probably did indeed ingest these seeds.

This case illustrates the importance of careful parental questioning about a child's dietary habits and particular picas when gastrointestinal problems are the chief complaint. It also illustrates one additional reason to strictly limit a child's accessibility to seeds as a dietary component.

J. Marshall Dent III, MD
Stanley I. Levine, MD, PhD
Department of Pediatrics
The Medical Center
710 Center St
Columbus, GA 31994-2299

1. Sleisenger M, Fordtan J. In: *Gastrointestinal Disease*. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1983:608.
2. Bockus HL, ed. *Gastroenterology*. 4th ed. Philadelphia, Pa: WB Saunders Co; 1985;2:1384-1385.
3. Melchreit R, McGownan G, Hyams J. 'Colonic crunch': sign of sunflower seed bezoar. *N Engl J Med*. 1984;310:1948-1949.

Passive Inhalation of Marijuana, Phencyclidine, and Freebase Cocaine ('Crack') by Infants

Sir:—Infants and toddlers appear to be highly susceptible to the toxic effects of smoke from pyrolyzed marijuana, phencyclidine, and freebase cocaine ("crack"). In the January 1989 issue of *AJDC*, Bateman and Heagarty[1] described the hospital course of four children who developed neurologic symptoms following passive inhalation of vaporized crack. Two of the four infants developed seizures. Accidental or deliberate exposure of infants to ambient marijuana or phencyclidine smoke in small smoke-filled rooms or in automobiles has been previously reported.[2,3] When irresponsible adolescents or young adults are intoxicated, they may, as a kind of sadistic "amusement," deliberately blow puffs of marijuana smoke into the noses or open mouths of crying irritable infants to sedate them.[2] Infants who ride in poorly ventilated automobiles with phencyclidine-smoking adults have developed frighteningly serious neurologic symptoms, such as coma or seizures.[3] It seems that urine toxicologic screening tests for drugs of abuse may be very informative in the evaluation of puzzling neurologic symptoms in infants.

Richard H. Schwartz, MD
410 Maple Ave W
Vienna, VA 22180

1. Bateman DA, Heagarty MC. Passive freebase cocaine ('crack') inhalation by infants and toddlers. *AJDC*. 1989;143:25-27.
2. Schwartz RH, Peary P, Mistretta D. Intoxication of young children with marijuana: a form of amusement for 'pot'-smoking teenage girls. *AJDC*. 1986;140:326.
3. Schwartz RH, Einhorn A. PCP intoxication in seven young children. *Pediatr Emerg Care*. 1986;2:238-241.

In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY

Autosomal Recessive Nonsyndromal Profound Childhood Deafness in a Large Pedigree: Audiometric Features of the Affected Persons and the Obligate Carriers

Henri A. M. Marres, MD, Cor W. R. J. Cremers, MD (*Arch Otolaryngol Head Neck Surg*. 1989;115:591-595)

Unintentional Poisoning Mortality—United States, 1980-1986

ALTHOUGH CHILDHOOD poisoning mortality has decreased in recent years, morbidity associated with poisoning in this age group remains a major public health problem. In 1987, 731,954 poisoning exposures among children less than 6 years of age were reported to the American Association of Poison Control Centers National Data Collection System; 22 of these children died, and 107,844 others became ill.[1] The number of exposures to household medicines and chemicals can be reduced by more widespread use of safety-packaged products by parents and other caretakers of children. The following report focuses on unintentional poisoning mortality among young adults, including poisonings from both the medical and nonmedical use of drugs.

Unintentional poisoning deaths in the United States were analyzed for 1980-1986 using final mortality data from CDC's National Center for Health Statistics (NCHS).* Age-adjusted mortality rates were directly standardized to the 1980 U.S. population.

From 1980 through 1986, the mortality rate of unintentional poisonings in the United States increased from 1.9 to 2.3 deaths/100,000 population. This 7-year trend appears to be explained by a 49% increase in the rate of deaths from drug poisoning, including drugs used for both medical and nonmedical purposes. Mortality rates of unintentional poisoning by other solids and liquids and by gases and vapors decreased by 15% and 25%, respectively, during 1980-1986. In 1986, the most recent year for which NCHS mortality data are available, drug poisonings accounted for 1.6 deaths/100,000 persons and 73% of all unintentional poisoning deaths.

In 1986, the leading causes of fatal unintentional drug poisonings were opiates and related narcotics and local anesthetics including cocaine. Most of the fatal poisonings by other solids and liquids were due to alcohol ingestion (352 deaths). Exposure to motor vehicle exhaust (475 deaths) accounted for nearly half the deaths due to unintentional poisoning by gases and vapors.

The mortality rate of unintentional poisonings for males remained more than twice that for females during 1980-1986. The rates for blacks of both sexes were consistently higher than those for whites. In 1986, the rate for black males was 5.4 deaths/100,000 persons, and for white males, 3.2 deaths/100,000 persons.

The highest mortality rates of unintentional poisonings for both blacks and whites were for young adult men (20-39 years of age). Men in this age group accounted for 40% of all unintentional poisoning deaths and 46% of all unintentional drug poisoning deaths during 1980-1986. In 1986, among young adult men, unintentional drug poisonings were responsible for 2065 deaths or 5.1 deaths/100,000 persons, an 85% increase from 1980.

In 1986, the leading causes of fatal unintentional drug poisonings for young adult men were opiates and related narcotics (619 deaths) and local anesthetics including cocaine (436 deaths). By comparison, in 1980, among young adult men, 213 deaths resulted from poisoning by opiates and related narcotics, and 73 deaths, from poisoning by local anesthetics including cocaine. In 1980 and 1986, additional deaths occurred among young adult men from unintentional poisonings by drug combinations, and an unknown number of these deaths involved opiates or cocaine.**

The mortality rate for unintentional poisonings among children less than 15 years of age was 0.3 deaths/100,000 persons in 1986, a 10% decrease from 1980. In 1986, 147 such deaths occurred among children less than 15 years of age, including 62 deaths from gases and vapors and 54 from drugs.

Reported by: Biometrics Br and Program Development and Implementation Br, Div of Injury Epidemiology and Control, Center for Environmental Health and Injury Control, CDC.
(MMWR vol. 38, No. 10)

CDC Editorial Note: Unintentional poisoning mortality is predominantly a problem of young adults, particularly men 20-39 years of age. NCHS data indicate that the misuse of drugs, primarily opiates and related narcotics and cocaine was responsible for a substantial increase in such deaths among men in this age group from 1980 through 1986. The impact of drug use on mortality is only partially conveyed by enumeration of unintentional poisoning deaths.[2] The mortality rate for young adult men rose during 1980-1986 for deaths attributed to drug dependence, nondependent drug abuse, and poisoning by drugs in which the intentions of the decedent are undetermined. For suicide by drugs, the mortality rate in young adult men remained nearly constant (1.6 deaths/100,000 persons in 1986) (NCHS, unpublished data).

The National Institute on Drug Abuse (NIDA) has reported increases in morbidity and mortality associated with nonmedical use of both heroin/morphine and cocaine during 1985-1987.[3] Through its Drug Abuse Warning Network (DAWN), NIDA monitors emergency departments and medical examiners' offices in selected locations for drug-related emergency visits and deaths. In 1987, cocaine was the most frequently reported drug involved in emergency visits, and heroin/morphine and cocaine each were involved in more than one third of deaths reported to DAWN. According to DAWN data for 1987, persons 20-39 years of age accounted for 70% of all drug-abuse emergency visits and 65% of all drug-abuse deaths.[4]

Reducing unintentional poisoning mortality among young adults requires prevention programs and treatment efforts that focus on the use of illicit drugs. Although medical complications of illicit drug use often emerge early in adulthood, initiation of drug use during adolescence is an impor-

tant risk factor for later hazardous use. This suggests that deterring or even delaying initiation of drug use among adolescents is an appropriate goal of prevention.[5] However, the recent increase in unintentional drug poisoning deaths among young adults underscores the need for drug education and treatment that focus on illicit drug users who are 20-39 years of age.

References

1. Litovitz TL, Schmitz BF, Matyunas N, Martin TG. 1987 annual report of the American Association of Poison Control Centers National Data Collection System. Am J Emerg Med 1988;6: 479-515.
2. Lettieri DJ, Backenheimer MS. Methodological considerations for a model reporting system of drug deaths. In: Josephson E, Carroll EE, eds. Drug use: epidemiological and sociological approaches. Washington, DC: Hemisphere Publishing, 1974.
3. National Institute on Drug Abuse. Semiannual report: trend data through July-December 1987—data from the Drug Abuse Warning Network (DAWN). Rockville, Maryland: US Department of Health and Human Services, Public Health Service, 1988. (Series G, no. 21).
4. National Institute on Drug Abuse. Annual data 1987: data from the Drug Abuse Warning Network (DAWN). Rockville, Maryland: US Department of Health and Human Services, Public Health Service, 1988. (Series I, no. 7).
5. Battjes RJ, Jones CL. Implications of etiological research for preventive interventions and future research. In: Jones CL, Battjes RJ, eds. Etiology of drug abuse: implications for prevention. Rockville, Maryland: US Department of Health and Human Services, Public Health Service, 1985; DHHS publication no. (ADM) 85-1335. (National Institute on Drug Abuse research monograph no. 56).

*NCHS codes the underlying cause of death according to the International Classification of Diseases (ICD). The ICD Ninth Revision (ICD-9) has been in use since the beginning of 1979. NCHS uses the ICD-9 codes E850-E858 for unintentional drug poisoning deaths, such as overdoses, regardless of whether the drug was administered for medical reasons. NCHS codes other drug-related deaths as deaths due to drug dependence (ICD-9 code 304), nondependent drug abuse (305.2-305.9), suicide by drugs (E950.0-E950.5), and poisoning by drugs in which the intentions of the decedent are undetermined (E980.0-E980.5).

**The ICD-9 code for unintentional poisoning by drug combinations is E858.8.

Scombroid Fish Poisoning—Illinois, South Carolina

SCOMBROID fish poisoning is an acute syndrome resulting from consumption of fish containing high levels of histamine. This report summarizes investigations of two outbreaks of scombroid fish poisoning in Illinois and South Carolina in 1988.

Illinois. On February 26, 1988, eight cases of scombroid fish poisoning occurred in Chicago in five patrons and three employees of a private club who had eaten a buffet lunch. Six of the ill persons experienced symptoms that included headache, nausea, flushing, dizziness, and diarrhea 90 minutes after the meal. The median duration of symptoms was 9.5 hours.

The club had purchased 10.5 pounds of frozen mahi mahi from a suburban Chicago distributor the week before it was served. The Food and Drug Administration (FDA) tested fish from 17 boxes in these lots; no fish from boxes with evidence of freezer burn were sampled. Six samples had histamine levels greater than or equal to 50 mg/ 100 g (range: 50-160 mg). The fish was kept in the club's freezer at 0-5 F (−15.0 C to −17.8 C) until February 26, when it was thawed by placing it under running water for 15 minutes. The fish was then cut into portions, placed flat in pans in the cooler, and baked as needed during lunch until the supply was depleted.

South Carolina. In September 1988, nine cases of scombroid fish poisoning in Charleston were investigated by the South Carolina Department of Health and Environmental Control.

The median age of the nine ill persons was 5 years (range: 18-64 years); five were women. Illness occurred 5-60 minutes after the meal (median time to onset of symptoms: 38 minutes). Symptoms included flushing, diarrhea, headache, feverishness, nausea, rapid pulse, pruritus, dizziness, vomiting, facial swelling, numbness around the mouth, and stomach pain. Symptoms resolved in all persons within 10 hours (median: 6 hours). Five patients required emergency room treatment, and one was admitted for observation because of underlying cardiac disease.

Two persons noted that the fish had a slight peppery taste and one person noted a metallic taste. All had eaten yellow-fin tuna supplied by the same local distributor. FDA analyses of two samples from the yellow-fin tuna revealed histamine levels of 728 mg/100 g and 583 mg/100 g, respectively.

CDC Editorial Note: During 1973-1986, 178 outbreaks of scombroid poisoning affecting 1096 persons (median: two cases/outbreak) were reported to CDC's Foodborne Disease Outbreak Surveillance System; no fatal cases were reported. Outbreaks have been reported from 30 states and the District of Columbia, with Hawaii reporting the largest number of outbreaks (51), followed by California (29), New York (24), Washington (19), and Connecticut (nine). The fish species was known in 143 (80%) of the scombroid outbreaks; the most commonly reported types were mahi mahi (66 outbreaks), tuna (42 outbreaks), and bluefish (19 outbreaks).

Scombroid poisoning is named for the family Scombridae, which includes tuna and mackerel, but this illness can occur after ingestion of any dark-fleshed nonscombroid species containing high levels of free histidine. When these fish are improperly refrigerated, free histidine is broken down to histamine by surface bacteria. This latter compound is thought to produce the clinical manifestations of illness, hence, some investigators have termed this syndrome histamine poisoning.

Illness begins minutes to hours after ingestion of the toxic fish. Symptoms resemble a histamine reaction and frequently include dizziness, headache, diarrhea, and a burning sensation or peppery taste in the mouth. Facial flushing, tachycardia, pruritus, and asthma-like symptoms can also occur. Illness is usually mild and duration is short, making treatment unnecessary. For more severe cases or in patients with underlying medical conditions, oral antihistamines may be beneficial. Intravenous cimetidine has been anecdotally reported to ameliorate symptoms but its use warrants further study.

When their recipe calls for allergy relief the twins take Tavist® Syrup

Tavist® Syrup contains the right ingredient to relieve allergies and keep the twins in the kitchen. One dose provides up to 12 hours of effective relief from symptoms of allergic rhinitis and mild urticaria.

Tavist® Syrup also has a convenient b.i.d. dosage to aid compliance, and a pleasant citrus taste even these master chefs can appreciate.

Prescribe the liquid allergy medicine that Pediatricians prescribe more than any other.* Prescribe Tavist® Syrup.

Tavist® Syrup. Lets kids be kids 12 hours long

(clemastine fumarate) 0.67mg/5ml

© 1989 Sandoz Pharmaceuticals Corporation

*National Prescription Audit, IMS America, LTD. Data on file, Sandoz Pharmaceuticals Corporation

Please see following page for brief summary of prescribing information.

TAS-489-2

BRIEF SUMMARY

TAVIST®

(clemastine fumarate) SYRUP 0.5 mg/5 ml
(present as clemastine fumarate 0.67 mg/5 ml)

INDICATIONS AND USAGE

Tavist® (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus and lacrimation. Tavist® (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see *DOSAGE AND ADMINISTRATION*).

It should be noted that Tavist® (clemastine fumarate) is indicated for the relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS

Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see *PRECAUTIONS — Drug Interactions* in a complete package insert).

Antihistamines should not be used in newborn or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see *PRECAUTIONS — Nursing Mothers* in a complete package insert).

WARNINGS

Antihistamines should be used with considerable caution in patients with: narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction.

Use with CNS Depressants: Tavist® (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.).

Use in Activities Requiring Mental Alertness: Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS

The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, hysteria, neuritis, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND RESPONSE OF THE PATIENT.

Pediatric: Children aged 6 to 12 years

For Symptoms of Allergic Rhinitis — The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 6 teaspoonsful daily (3 mg clemastine).

For Urticaria and Angioedema — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and Over

For Symptoms of Allergic Rhinitis — The starting dose is 2 teaspoonsful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (6 mg clemastine).

For Urticaria and Angioedema — The starting dose is 4 teaspoonsful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED

Tavist® (clemastine fumarate) Syrup

Clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor, in 4 fl. oz. bottle (NDC 0078-0222-31).

[TAS-Z3 APRIL 1, 1986]

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

First and second year Osteopathic Pediatric residency positions are available at Grandview Hospital in Dayton, Ohio. This is a didactic program with a wide and varied caseload. Opportunity for appointment to the attending staff at the completion of the training program is available. For further information please contact:

H. Lauren Vogel, D.O.
DME at Grandview Hospital
405 Grand Avenue
Dayton, OH 45405-4796
or (513) 226-3247

HOUSE BASED PEDIATRICIANS (HBPs)

Huntington Memorial Hospital of Pasadena, California, a major affiliate of the University of Southern California School of Medicine, is seeking to hire four board eligible/certified pediatricians by July 1, 1989 to cover its 34-bed pediatric floor. These four house-based pediatricians (HBPs) will provide in-house coverage that traditionally would have been provided by pediatric interns or residents.

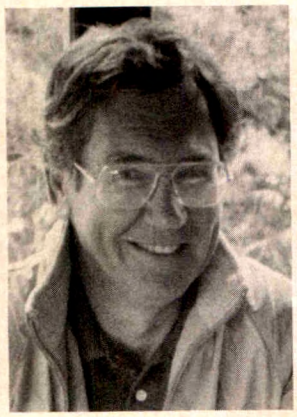
Founded in 1892, Huntington Memorial Hospital is a 606-bed non-profit medical center that serves the communities of the San Gabriel Valley of Los Angeles County. The total service area population of the San Gabriel Valley is approximately two million people. The Hospital offers a tertiary Infertility Center, Perinatal High-Risk Unit, a Neonatal ICU and renowned ECMO Center, a comprehensive Pediatric Center and a Pediatric ICU.

The compensation is competitive with the HMOs or other salaried positions in the area: $70,000 annual salary; health insurance (medical, dental, vision); life insurance ($50,000 term life); accidental death & dismemberment ($50,000); paid 3-week vacation; and a $1000 annual CME fund.

Those interested should send their CV and inquiries to Edgardo L. Arcinue, M.D., Head, Department of Pediatrics, 100 Congress Street, Pasadena, CA 91105; (818) 397-8688.

The Editorial Board Speaks . . .

Barton D. Schmitt, MD



"Bart," Mary, and their family have had an eventful year, both personally and professionally. Their youngest teenager has entered college at Lewis and Clark, Portland, Ore, resulting in the "empty nest" syndrome, both enjoyed and lamented. While another offspring attends Pomona College in Claremont, Calif, their two oldest work in the Denver, Colo, area, so the separation is not absolute.

Professionally, Bart's book, *Your Child's Health* (New York, NY: Bantam Books Inc; 1987) has enjoyed excellent reviews and successful sales. It is a practical pediatric guide for parents with useful advice on health and disease. In addition, Bart has coedited, with Donald Bross, JD, Richard Krugman, MD, Marilyn Lenherr, MS, and Donna Rosenberg, MD, *The New Child Protection Team Handbook*.

NIGHTMARES ON MAIN STREET

I confess. I love the movies—almost all movies. But, if you want a good night's sleep, skip those mad slasher movies. They're made to frighten adults, and they work. So, who sees these flicks? Children. And that's when the nightmares, bedtime fears, and other sleep problems in my patients commonly begin:

An 8-year-old girl begins to have nightly terrifying dreams after seeing *Nightmare on Elm Street*. The content of her dream is that Freddy Kruger catches her and tears her head off. She saw the movie with her 16-year-old brother, who rented it while he was babysitting.

A 5½-year-old girl has a 3-month history of nightmares in which she is pursued and killed by Jason. She saw *Friday The 13th* the day before the onset. She watched it on cable television while staying overnight with a friend. They got up and turned it on after the parents went to bed.

A 3-year-old is watching *E.T.* with his family. He runs screaming from the room the first time E.T. appears on the screen. He is not able to sleep alone again for the next 6 months.

The content of violent movies has changed over the last 10 years. Mutilation is the message. Thanks to improved special effects, we can now see the details of violence in slow, agonizing close-up. Recent movies show a head being chopped off, a brain being blown up, the disfigurement of a face with a knife, a neck being slashed, or a hypodermic needle being inserted into the eyeball. Would these disgusting images unsettle your child? You do not need to be a child psychologist to know the answer.

Access to these violent movies has also changed. Parents say "I didn't know they were watching that. I can't keep track of everything they see." The uncut versions of violent movies are now readily available through cable television and video rentals. A popular party game in junior high school involves renting a horror movie and seeing how much of it your friends can watch before becoming ill. Even network television carries some movies disturbing to children (eg, *The Day After*).

Children do not have the adult thought processes and defense mechanisms needed to cope with movie violence. Many children younger than 7 or 8 years old are unable to distinguish reality from fantasy. Even monsters (E.T.?) scare them. Young children also think concretely ("If it can happen to them, it can happen to me"). Children of all ages are threatened by movie villains who seem real and play on their deepest fears (eg, attack, kidnapping, pain, or death). Some of these slashers (unlike real people) are portrayed as indestructible and leave the young viewer feeling helpless. In particular, Freddy Kruger perpetrates the greatest insomnia because he kills children by entering their dreams. Some children who watch this movie become afraid to sleep and dream.

Here are some recommendations to help protect children from violent R-rated movies:

1. Help parents understand that we cannot lump all R-rated movies together. The R-rating means that children under 17 years are not admitted without a parent. It is given for nudity, profanity, violence, or a combination of the above. Nudity, depending on the context, may be harmless. Profanity in the movies has contributed to the common use of profanity on elementary school playgrounds. It is doubtful that this trend can be reversed at this late date. It is the violence in the movie that has the disturbing impact on children. In fact, if one reads the ratings carefully, the degree of violence is also often listed (eg, "graphic" violence).
2. Tell parents that R-rated, violent movies frighten children and cause bedtime fears, nightmares, and a fearful view of the world.
3. Tell parents never to allow a child who is less than 13 years of age to see any R-rated violent film, no matter how liberal they may be about nudity and profanity. Between 13 and 17, the maturity and sensitivity of the child must be carefully considered.
4. When their child reaches age 3 or 4 years, mention to the parents how important it is to protect their child from being victimized by film violence. (Beware of slumber parties or Halloween parties.)
5. The movie industry will be the first to state that they have not produced R-rated movies for children. However, for the forgetful parent, they need to put a strong warning (not the current token definition of R-rated) at the entrance to the theater and on the screen at the start of the movie regarding the specific content (eg, graphic deaths or rape).
6. Movie theaters should sell tickets to R-rated movies only to people over 17 years of age.
7. The ushers in the movie theaters should reroute children who sneak into another movie after admission.
8. We need laws that ban the rental or sale of violent movies to anyone under 17 years of age. Sales people in video stores must check IDs, and there should be a penalty for violations.

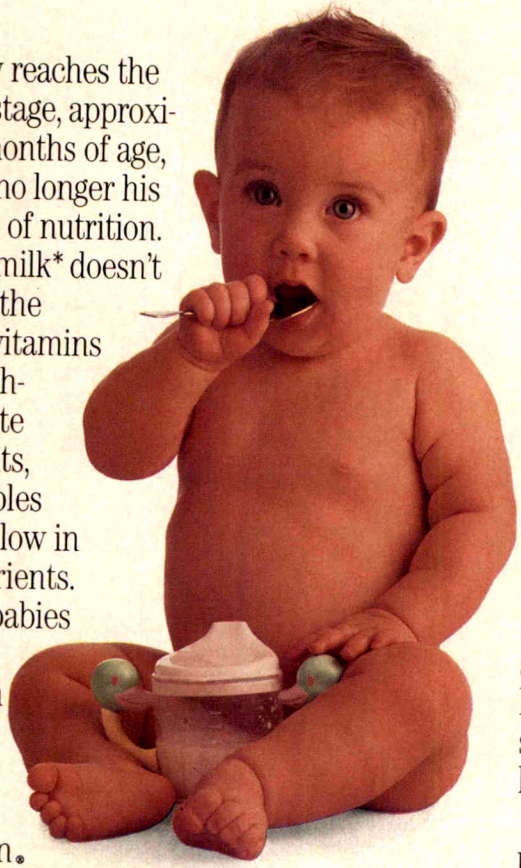
The kinds of fears engendered by grizzly, gory movies can persist for months or years. It is the parents' responsibility to control what movies their children are watching. It is our responsibility to remind them of the importance of this issue.

CARNATION®

GOOD NATURE™

Iron Fortified Follow-Up Formula

For babies over six months of age eating solid foods



When baby reaches the solid food stage, approximately 6 months of age, formula is no longer his sole source of nutrition. Yet, whole milk* doesn't contain all the necessary vitamins and the high-carbohydrate cereals, fruits, and vegetables he eats are low in certain nutrients. And, older babies require less energy from fat[1] and more from protein.[2]

Carnation® GOOD NATURE™ Follow-Up Formula provides the added nutrients for the older baby's optimal growth and development. And it contains more protein and calcium than starter formula to support the increased metabolic demands of bone mineralization and muscle mass growth.

The ratio of unsaturated to saturated fatty acids in GOOD NATURE is 2:1. GOOD NATURE is higher in monounsaturated fatty acids yet contains 28% less fat than starter formula to satisfy the changing needs of the older baby.

GOOD NATURE also has a carbohydrate blend of 63% corn syrup solids and 37% lactose to help assure tolerance. It contains 12 mg iron per quart to help ensure a sufficient supply at an age when inborn stores are depleted. GOOD NATURE costs less than starter formula and also tastes, smells, and looks like the real food baby is learning to enjoy.

When baby is ready for solid food, Mom may ask you about GOOD NATURE Follow-Up Formula. You can reassure her that GOOD NATURE is nutritionally sound and makes good sense for her baby.

For more information about GOOD NATURE Follow-Up Formula, please write to:
Carnation Nutritional Products,
5045 Wilshire Blvd., Los Angeles, CA 90036.

Carnation®
Setting the stage for better development™

GOOD NATURE Follow-Up Formula... now available to consumers in 32-fl-oz ready-to-feed fresh packs and 12-oz easy-to-mix powder canisters.

REFERENCES: 1. Kwiterovich PO Jr, Salz KM: Pediatric aspects of the diet-heart hypothesis, in Bond JT, Filer LJ, Leveille GA, et al (eds): *Infant and Child Feeding.* Academic Press, 1981, pp 283-315.
2. Food and Nutrition Board, NAS/MRC. *Recommended Dietary Allowances,* ed 9, 1980. *Pasteurized cow's milk.

NP-026 3/89

Editorial

Cleveland, England

Child Abuse in the Public Eye

A major problem has developed in England that may have profound effects on the practice of pediatrics, particularly in relation to identification of child abuse. Two pediatricians, Dr Marietta Higgs and Dr Geoffrey Wyatt, working in Cleveland, England, identified a series of children as potential victims of child abuse. In so doing, they relied heavily on a sign described by Hobbs and Wynne[1] in *Lancet* in 1986, reflex anal dilatation. This sign is elicited by stroking the skin near the anus and observing dilatation instead of puckering. The claim is made that such dilatation reflects anal penetration, hence sexual abuse of the child in question. The two pediatricians claim that the sign was only part of their assessment, and that other signs and historical data were also used in their diagnosis. The public claimed otherwise.

The problem became a public issue when the number of patients identified as being potentially abused soared in 1986. Parents and one member of Parliament from the district protested; many public stories appeared in the press and in a book written by the member of Parliament. The result was a public clamor for action, which resulted in the appointment of a blue-ribbon panel, headed by Lord Justice Butler-Sloss. This panel reported in June 1988 with broad recommendations and findings.[2] Although they took the pediatricians to task in their report for overdiagnosis and overreliance on the one sign of reflex anal dilatation, the press coverage and other media approaches took a dim view of the diagnosis of child abuse. Almost lost in the furor was the major recommendation of the Butler-Sloss panel, which suggested that there was a need for data on the prevalence and nature of child abuse in England.

This précis of the events does not do justice to the attention given the issue in England at the time. Virtually every newspaper carried extensive stories on the Cleveland events; interviews with the member of Parliament, with parents, and with the two pediatricians and other health and welfare workers were evident daily on television; and the panel's report was given wide, if selective, coverage that included snippets of the presentation of the report by the distinguished jurist and her panel. The commentaries on television and the editorials appeared to have the thrust of downplaying the possibility that so many children could have been abused, and that the two pediatricians were "arrogant" in their insistence that they were diligent and correct in their assessments. We were in England at the time and for almost 2 weeks, virtually every front page and every newscast and talk show featured some aspect of this story.

Now comes a lead editorial in *Lancet* in which the matter is reviewed briefly once again, and the conclusion is reached that "By their bull-headed approach, Dr. Higgs and Dr. Wyatt, however, have set back the cause they sought to promote."[3] The editorial characterizes the two doctors as being "naive" at best. Lost in the myriad of public pronouncements, including the piece in *Lancet*, is the possibility that the physicians were correct, ie, that abuse was rampant in their practice. Certainly we have learned in the United States that the problem is not a minor one, and that thousands of children suffer each year and many die of the effects of abusive behavior by parents, guardians, and other "care givers." Our concern is that the popular and parliamentary response in England may set back the cause of protecting children. Henry Kempe, during his lifetime, recognized the forces in society that tend both to deny abuse as a possibility and to prevent exploration of the issue.[4] In Kempe's day police, judges, social workers, and others thought that his pioneering descriptions of child abuse were "overdrawn" and not possible. Parents were thought not to abuse their children and it took years from publication of Kempe's[2] epochal article in *JAMA*[5] for the reality of abuse to take root in American thought and in medical practice. Even today, there are some who believe that pediatricians overdo this aspect of their practices.

England may have been set back not because the physicians were overzealous, but because the public reaction resulted in an impression that child abuse could not possibly be that prevalent. We do not know the facts; even the *Lancet* article states that "even now, who knows how many of the Cleveland children were abused." The distinct impression of the public media and of the panel is that diagnosis was overdone and that the physicians relied soley on the reflex anal dilatation sign as evidence for abuse, their public statements to the contrary notwithstanding. Yet, while outcomes are not presented, the samples described in the report indicate that the *majority* of the children *were* abused. Any assumption that being returned home is the same as not being a victim without more information on what transpired in court is an erroneous interpretation of child welfare practice. The Butler-Sloss panel report is very comprehensive, did dissect the complex issues involved, and pointed the way to better data collection and a more orderly approach to case management, which was another criticism of the system employed in Cleveland. Most poignantly, the report noted that "The children were never heard." Those who *were* abused were not heard by the public; those who *were not* abused

were not heard by the professionals. Also included in the report is a recommendation for research into the physical signs of child abuse, for specialist assessment teams to work in tandem with referrals of potential child abuse victims, and for a balanced judicial procedure in adjudicating the claims of abuse, taking into account the parents' as well as the children's interests. The Standing Medical Advisory Committee (SMAC) and the Standing Nursing and Midwifery Advisory Committee of the DHSS in England have issued professional guidelines to supplement the panel's report.[6,7]

We have learned in the United States that there is no substitute for clinical competence in the multidisciplinary approach. The key failure of this approach in Cleveland was that the physicians saw a sign (reflex anal dilatation) that made them suspect abuse, and the social workers who did "disclosure work" equated a negative history with "denial." As David Jones said in the Butler-Sloss report: "The problem with 'disclosure work' is that it presumes there is something to disclose." Regretfully, the emotions aroused on both sides of the issue of sexual abuse in both countries do not easily permit one to say "we don't know."

One hopes that these positive aspects of the issue would not be overshadowed by a public suppression of the diagnosis and management of children who are abused. As the *Lancet* editorial states, "The SMAC recommends that if parental consent to medical assessment and examination is withheld, then social services must consider court proceedings; however, the views of the child, if competent, are paramount."[3,6] This recommendation echoes the sentiments of Dr Kempe, who frequently stated that one should avoid the charge/countercharge milieu by declaring the child "underprotected," which then would permit calm and judicious investigation, during which the child could be protected from possible additional abuse.

The English experience also emphasizes the differing nature of public awareness of abuse and social thought in the two countries. We have come to accept the problem as a real one, recognize and report over 1% to 2% of children each year, and have difficulty in applying the necessary resources in many jurisdictions because of limited funding. Our own observation of the cases seen in Leeds, England (by Hobbs and Wynne, who are the mentors of Higgs and Wyatt), is that they are seeing the "battered children" of sexual abuse. In contrast to the situation in the United States, where public *and* professional awareness is so high that we see sexual abuse cases early, usually with no physical findings, in the United Kingdom awareness is so low, even among professionals, that only the most obvious and chronic cases are referred. Apparently, England is just now recognizing that the problem must be addressed, but the negative nature of the Cleveland episode could result in public backlash that may set back the cause of child welfare; only attention to the positive recommendations of the Butler-Sloss panel can produce a balanced view. We hope our colleagues in pediatric practice in England will succeed in maintaining the interests of the child as "paramount," as the SMAC suggests.

VINCENT A. FULGINITI, MD
Editor, *AJDC*
Dean's Office, Room 1529
Tulane University
School of Medicine
1430 Tulane Ave
New Orleans, LA 70112

RICHARD D. KRUGMAN, MD
Director, The C. Henry Kempe
National Center for the
Prevention and Treatment
of Child Abuse and Neglect
1205 Oneida St
Denver, CO 80220

References

1. Hobbs DJ, Wynne JM. Buggery in childhood: a common syndrome of child abuse. *Lancet.* 1986;2:792-796.
2. *Report of the Inquiry Into Child Abuse in Cleveland, 1987.* London, England: 1988.
3. Child Abuse after Cleveland. *Lancet.* 1988; 2:139-140. Editorial.
4. Helfer RE, Kempe CH. *The Battered Child.* Chicago, Ill: University of Chicago Press; 1968.
5. Kempe CH, Silverman FN, Steele BF, Droegemueller W, Silver HK. The battered child syndrome. *JAMA.* 1962;181:17-20.
6. *The Diagnosis of Child Sexual Abuse: Guidance for Doctors.* London, England: Her Majesty's Stationery Office; 1988.
7. *Child protection: Guidance for Senior Nurses, Health Visitors and Midwifes.* London, England: Her Majesty's Stationery Office; 1988.

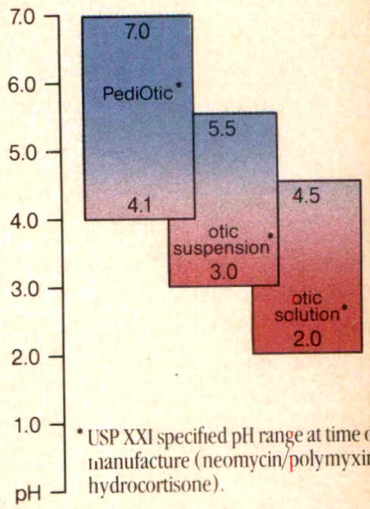
In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY
Clinical Experience With Electroneurography in the Pediatric Patient
Roland D. Eavey, MD; Barbara S. Herrmann, PhD; Janet M. Joseph, MS; Aaron R. Thornton, PhD (*Arch Otolaryngol Head Neck Surg.* 1989;115:600-607)

PediOtic® suspension sterile

Formulated to be less acidic to help minimize irritation.

A more normal pH range means less potential for painful irritation.



* USP XXI specified pH range at time of manufacture (neomycin/polymyxin B hydrocortisone).

Formulated to help take the sting out of otitis externa therapy

PediOtic suspension is specially formulated to have a higher pH range than conventional otics.

Children may be less likely to resist its instillation, and their parents will appreciate the ease of compliance.

And you can prescribe PediOtic suspension with confidence, knowing it contains the same proven antibiotic/anti-inflammatory combination physicians have trusted for years.

Now there's a gentle effective treatment for "swimmer's ear" to please patient, parent, *and* physician.

Please see brief summary of prescribing information on next page.

PediOtic® suspension sterile

Wellcon

(polymyxin B sulfate-neomycin sulfate-hydrocortisone)

PediOtic® suspension sterile

(polymyxin B sulfate-neomycin sulfate-hydrocortisone)

DESCRIPTION: Pediotic suspension (polymyxin B sulfate-neomycin sulfate-hydrocortisone) is a sterile antibacterial and anti-inflammatory suspension for otic use. Each ml contains: Aerosporin® (polymyxin B sulfate) 10,000 units, neomycin sulfate equivalent to 3.5 mg neomycin base, and hydrocortisone 10 mg (1%). The vehicle contains thimerosal 0.001% (added as a preservative) and the inactive ingredients cetyl alcohol, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, propylene glycol, and Water for Injection. Sulfuric acid may be added to adjust pH. Pediotic suspension has a minimum pH of 4.1, which is less acidic than the minimum pH of 3.0 for Cortisporin® Otic Suspension.

INDICATIONS AND USAGE: For the treatment of superficial bacterial infections of the external auditory canal caused by organisms susceptible to the action of the antibiotics, and for the treatment of infections of mastoidectomy and fenestration cavities caused by organisms susceptible to the antibiotics.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components, and in herpes simplex, vaccinia, and varicella infections.

WARNINGS: This product should be used with care in cases of perforated eardrum and in longstanding cases of chronic otitis media because of the possibility of ototoxicity. Neomycin sulfate may cause cutaneous sensitization. A precise incidence of hypersensitivity reactions (primarily skin rash) due to topical neomycin is not known. When using neomycin-containing products to control secondary infection in the chronic dermatoses, such as chronic otitis externa or stasis dermatitis, it should be borne in mind that the skin in these conditions is more liable than is normal skin to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low-grade reddening with swelling, dry scaling and itching; it may be manifest simply as a failure to heal. Periodic examination for such signs is advisable, and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for the patient thereafter.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi.

If the infection is not improved after one week, cultures and susceptibility tests should be repeated to verify the identity of the organism and to determine whether therapy should be changed.

Treatment should not be continued for longer than ten days.

Allergic cross-reactions may occur which could prevent the use of any or all of the following antibiotics for the treatment of future infections: kanamycin, paromomycin, streptomycin, and possibly gentamicin.

ADVERSE REACTIONS: Neomycin occasionally causes skin sensitization. Ototoxicity and nephrotoxicity have also been reported (see WARNINGS section). Adverse reactions have occurred with topical use of antibiotic combinations including neomycin and polymyxin B. Exact incidence figures are not available since no denominator of treated patients is available. The reaction occurring most often is allergic sensitization. In one clinical study, using a 20% neomycin patch, neomycin-induced allergic skin reactions occurred in two of 2,175 (0.09%) individuals in the general population.[1] In another study, the incidence was found to be approximately 1%.[2]

The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria. Stinging and burning have been reported rarely when this drug gained access to the middle ear.

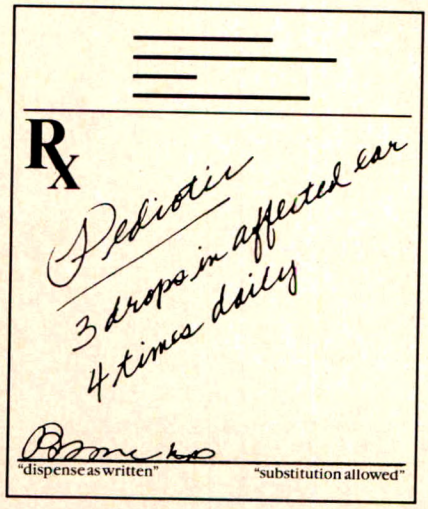
HOW SUPPLIED: Bottle of 7.5 ml with sterilized dropper. NDC 0081-0910-02. Store at 15° to 25°C (59° to 77°F).

REFERENCES: 1. Leyden JJ, Kligman AM: Contact dermatitis to neomycin sulfate. *JAMA* 1979;242:1276-1278. 2. Prystowsky SD, Allen AM, Smith RW, et al: Allergic contact hypersensitivity to nickel, neomycin, ethylenediamine, and benzocaine. *Arch Dermatol* 1979;115:959-962.

BURROUGHS WELLCOME CO., Research Triangle Park, NC 27709

Copr. © 1989 Burroughs Wellcome Co. All rights reserved.

PED-101R



Formulated to help take the sting out of otitis externa therapy.

INDEX TO ADVERTISERS

Allen & Hanburys, Division of Glaxo, Inc. 704A-D, 705

Burroughs Wellcome Company 653-654

Carnation Company 650
Christie Clinic Association 672

Falls Church Medical Center 636
Fisons Corporation 671-672

Grandview Hospital 648

Huntington Memorial Hospital 648

ICN Pharmaceuticals, Inc. 636A-D, 637

Jackson Memorial Hospital 730

Lederle Laboratories 631-632, 729-730, 752

McNeil Consumer Products Company 697
Mennen Company .....Cover 2
Merieux Institute, Inc. 635

National Biological Corporation 730
New Hanover Memorial Hospital 746

Rorer Pharmaceuticals 745-746

Sandoz Pharmaceuticals ..... 647-648, Cover 3

University of Kansas 746
University of New Mexico 636

Wyeth-Ayerst Laboratories .....Cover 4

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Articles

Efficacy and Immunogenicity of Acellular Pertussis Vaccine by Manufacturer and Patient Age

Tatsuo Aoyama, MD, MPH; Yuji Murase, MD; Makoto Kato, MD; Hideto Iwai, MD; Takashi Iwata, MD

• **Acellular pertussis vaccines, which have been used in Japan since 1981, vary in antigenic constituents among manufacturers. First, to assess the immunogenicity by manufacturer and patient age, 161 children aged 3 months to 2 years were immunized by acellular pertussis vaccine from one of three Japanese manufacturers, Biken, Takeda, or Kitasato. Anti–pertussis toxin antibody responses for children immunized with Takeda and Kitasato vaccines were comparable with patients with pertussis in the convalescent stage, and anti–pertussis toxin antibody response for Biken vaccine was far higher than those of convalescing patients. Anti–filamentous hemagglutinin antibody responses for the children given the three vaccines were far higher than those of the patients. Weak serotype 1.3 agglutinin responses were observed only in children administered the Takeda vaccine. Comparing these antibody responses among various age groups, the immunogenicity of acellular vaccines in children aged 3 to 6 months was comparable with children aged 2 years. Second, to assess the manufacturer-specific efficacy, 495 households of patients with pertussis were surveyed from 1981 to 1988. The estimated efficacy of the acellular pertussis vaccines in children aged 2 to 8 years was 82%, and there were no major differences in the secondary attack rates among children immunized with acellular pertussis vaccine from each manufacturer, ie, 12.5% (1/8) for Biken, 11.1% (2/18) for Takeda, and 5.9% (1/17) for Kitasato. We conclude from these two studies that similar efficacy was observed in children aged 2 years or older for acellular pertussis vaccines from the three manufacturers, which produced anti–pertussis toxin antibody responses comparable with patients with pertussis and far higher anti–filamentous hemagglutinin antibody responses than in the convalescing patients, and that age did not affect the immunogenicity of acellular vaccines.**

(*AJDC*. 1989;143:655-659)

Acellular diphtheria, tetanus, and pertussis (DTP) vaccines containing components of acellular pertussis vaccine have been used in Japan since 1981 with the aim of reducing adverse reactions associated with previously used whole-cell vaccines. Since its introduction, a decline in pertussis cases has been noted. At the time of their introduction, the only requirement of efficacy for Japanese acellular pertussis vaccines was their potency, which was determined by the modified intracerebral mouse protection test.[1] Because of this modification, the assigned potency is higher than the potency calculated by the standard test recommended by the World Health Organization.

With improved characterization of antigens, it has become clear that the content for pertussis toxin (PT), filamentous hemagglutinin (F-HA), and agglutinogens of acellular vaccines prepared by a particular manufacturer was constant over several years, but differed from vaccines prepared by other manufacturers.[2,3] Acellular pertussis vaccines have been produced by six Japanese manufacturers: Biken (The Research Foundation for Microbial Diseases of Osaka University), Takeda (Takeda Chemical Industries, Osaka), Kitasato (The Kitasato Institute, Tokyo), Chiba (Chiba Serum Institute, Ichikawa), Denka (Denka Seiken Co, Tokyo), and Kaketsu (Chemo-Sero-Therapeutic Institute, Kumamoto). Several clinical trials with Japanese acellular vaccines are under way: acellular vaccine produced by Biken has been studied in Sweden,[4,5] and acellular vaccine by Takeda has been studied in the United States.[6-8] These trials proved that Japanese acellular vaccines are much less reactogenic than whole-cell pertussis vaccines and that Japanese acellular pertussis vaccines are at least as immunogenic as whole-cell vaccines.

However, there are no data available comparing manufacturer-specific immunogenicity and efficacy, and, at present, it is not clear what the most ideal composition of acellular pertussis vaccine is in terms of immunogenicity and efficacy. Therefore, it is very important to assess the immunogenicity and efficacy of acellular vaccine with various composition. In addition, the efficacy data in Japan do not include children less than 2 years of age, because the majority of children start to receive DTP vaccine at the age of 2 years. We compared the immunogenicity of acellular pertussis vaccine from three manufacturers and examined the immunogenicity of acellular DTP vaccine by age to predict the efficacy in children younger than 2 years old. We have also used our ongoing household survey to assess the efficacy of acellular pertussis vaccines by manufacturer.[9,10]

PATIENTS AND METHODS

First, to investigate the immunogenicity of acellular pertussis vaccine, healthy children from a special residential facility between the ages of 3 months and 2 years were enrolled in the study after informed consent was obtained from their guardians. These children received three primary doses of acellular DTP vaccine every 4 weeks and one booster dose 6 months after the last of the primary series. Each injection of 0.5 mL was given deeply into the subcutaneous tissue of the deltoid region. A total of five lots of com-

Accepted for publication January 3, 1989.

From the Department of Pediatrics, Keio University, School of Medicine, Tokyo, Japan.

Presented at the Workshop on Acellular Pertussis Vaccine, National Institutes of Health, Bethesda, Md, February 9, 1988.

Reprint requests to Pediatric Department, Keio University, School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160 Japan (Dr Aoyama).

mercially available acellular DTP vaccine from three different manufacturers were used: lots 11 and 17 from the Research Foundation of Microbial Diseases of Osaka University (Biken), lots 15 and 20 from Takeda Chemical Industries (Takeda), and lot 17 from the Kitasato Institute (Kitasato) (Table 1).

One hundred forty-nine children aged 3 to 23 months and 12 children aged 2 years were enrolled in this study (Table 2). The 12 children aged 2 years received Kitasato lot 17. The number of children aged 3 to 11 months when the first dose was given was almost the same as that of children aged 12 to 23 months.

Blood was drawn by venipuncture before the first immunization and 4 weeks after the last of the primary series. Blood also was obtained before the booster and 4 weeks after the booster. Agglutinin titer for serotype 1.3 strain was measured by the microagglutination test, the procedure of which was essentially the same as that described by Manclark and Meade.[11] Antibodies to PT and F-HA were determined by an indirect glass bead enzyme-linked immunosorbent assay.[12]

Second, to investigate the efficacy of acellular pertussis vaccine, all cases of suspected pertussis seen at Keio University Hospital, Tokyo, and its affiliated hospitals located in the Tokyo metropolitan area from 1981 to 1988 were reported to us. From these reports, patients with pertussis were selected by the following criteria: characteristic paroxysmal coughing attacks commonly seen in pertussis, which last for more than 2 weeks, and at least one of the four following conditions: (1) nasopharyngeal culture positive for *Bordetella pertussis*; (2) peripheral white blood cell count of 15×10^9/L or greater, with more than 0.70 lymphocytes; (3) bacterial agglutinin titer of serotype 1.3 increased at least fourfold; or (4) agglutinin titer of 40 or greater (excluding vaccinated individuals).

Using the above criteria, 495 households of patients with pertussis qualified. In 196 (39.6%) of the 495 households, at least one patient with culture-verified pertussis was identified.

For the purposes of this article, terms were defined as follows:

1. *Primary case*: the first person who developed a paroxysmal cough that lasted for more than 2 weeks in a household with pertussis.

2. *Secondary case*: any person in a household who developed a paroxysmal cough that lasted for more than 2 weeks, with symptoms occurring 1 to 4 weeks after the onset of symptoms in the primary case.

3. *Coprimary case*: any person in a household who developed a paroxysmal cough that lasted for more than 2 weeks, with symptoms occurring within 1 week of the onset of symptoms in the primary case.

Table 1.—Pertussis Content of Acellular DTP*

Manufacturer and Lot No.	Pertussis Antigen	PT	F-HA	Agglutinin	Aluminum, g/L
Biken					
11	12.0	6.0	6.0	. . .	0.20
17	10.0	5.0	5.0	. . .	0.15
Takeda					
15	14.6	1.5	12.3	0.4	0.20
20	12.1	1.3	10.3	0.3	0.20
Kitasato					
17	14.0	1.4	11.9	. . .	0.15

*Data were provided by each manufacturer. DTP indicates diphtheria, tetanus, pertussis; PT, pertussis toxin; and F-HA, filamentous hemagglutinin. Values are milligrams of protein nitrogen per liter unless otherwise stated.

Table 2.—Number of Children Who Received Three Primary Doses by Lot of Acellular DTP and Age When the First Dose Was Given*

	Takeda		Biken		
Age, mo	Lot 15	Lot 20	Lot 11	Lot 17	Kitasato Lot 17
3-11	10	15	8	8	38
12-23	13	10	10	6	31
Total	**23**	**25**	**18**	**14**	**69**

*Twelve children aged 24 to 35 months also received Kitasato lot 17. DTP indicates diphtheria, tetanus, pertussis.

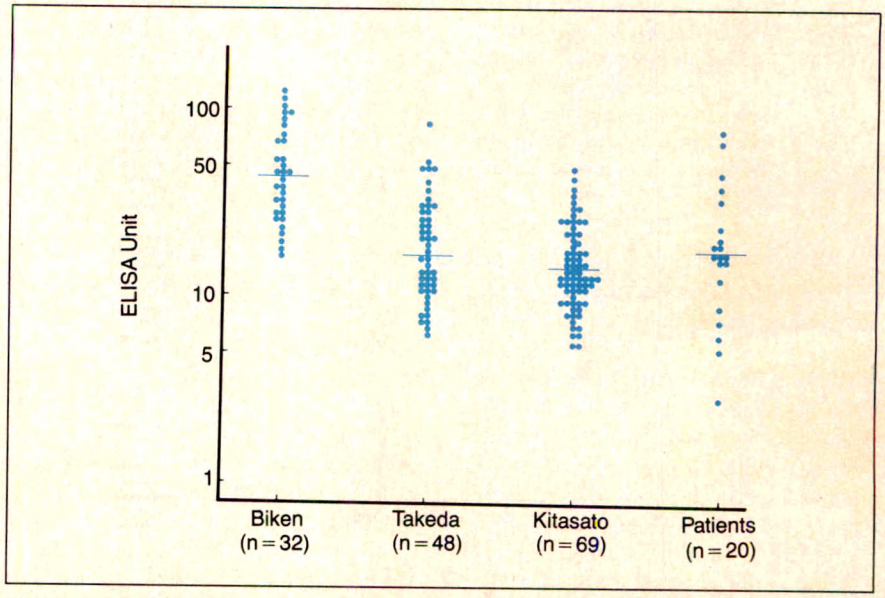


Fig 1.—Comparison of anti–pertussis toxin antibody in children given three primary doses of acellular diphtheria, tetanus, and pertussis vaccine from one of the three manufacturers at 4 weeks after the last of the primary series, and patients with pertussis in the convalescent stage. ELISA indicates enzyme-linked immunosorbent assay; bar, geometric mean.

4. *Vaccination status*: with three or four DTP injections, the child was considered fully immunized; with one or two DTP injections, partially immunized.

The information about the household of each patient with pertussis was obtained either by an interview in the clinic or by telephone. This information concerned patient

symptoms, the vaccination status of all children, and the occurrence of any primary, coprimary, or secondary cases. Information concerning the manufacturer and lot of DTP injections given after September 1981 was obtained from local governments, local health centers, or local health associations that had supervised the vaccinations.

The χ^2 test was used to evaluate the statistical significance of differences between proportions, and the Student t test was used to determine the significance of differences between geometric means.

RESULTS

Immunogenicity of Acellular Pertussis Vaccine

Anti-PT and anti–F-HA antibody levels in children younger than 2 years of age 4 weeks after the third dose of primary injections of acellular DTP vaccine were compared with the antibody levels of 20 patients younger than 2 years of age who had had culture-verified pertussis for 6 to 10 weeks (Figs 1 and 2). The geometric mean of anti-PT antibody for Biken lots 11 and 17 was 2.5 times higher than that of patients with pertussis in the convalescent stage ($P<.01$). The geometric mean of anti-PT antibody for Takeda lots 15 and 20 and Kitasato lot 17 was almost as high as that of patients with pertussis. The geometric mean of anti–F-HA antibody responses for Biken lots 11 and 17 and Kitasato lot 17 was six times higher than that of patients with pertussis ($P<.01$). The geometric mean of anti–F-HA antibody responses for Takeda lots 15 and 20 was eight times higher than that of patients with pertussis ($P<.01$).

Anti-PT and anti–F-HA antibody levels 4 weeks after the booster were similar to the antibody levels 4 weeks after the three primary doses for the three manufacturers. The differences in antibody responses between the three manufacturers were also observed before the booster and at 4 weeks after the booster immunization. There was no difference in antibody responses between Takeda lot 15 and lot 20, and no difference between Biken lot 11 and lot 17.

No serotype 1.3 agglutinin responses were observed 4 weeks after the three primary injections of Biken lots 11 and 17 and Kitasato lot 17. The geometric mean of serotype 1.3 agglutinin responses 4 weeks after the three primary injections of Takeda lots 15 and 20 was half as high as that of patients with pertussis ($P<.01$) (Fig 3).

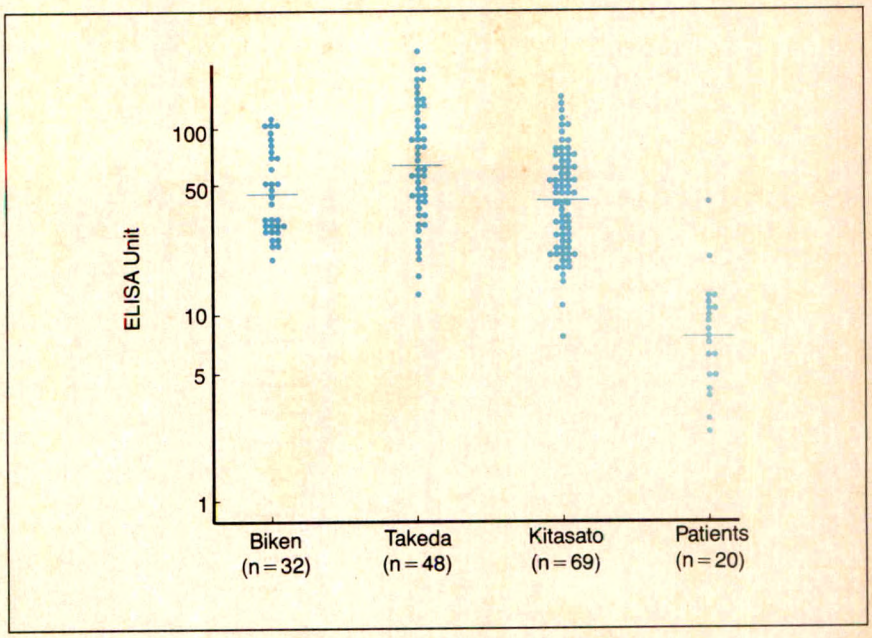


Fig 2.—Comparison of anti–filamentous hemagglutinin antibody in children given three primary doses of acellular diphtheria, tetanus, and pertussis vaccine from one of the three manufacturers at 4 weeks after the last of the primary series, and patients with pertussis in the convalescent stage. ELISA indicates enzyme-linked immunosorbent assay; bar, geometric mean.

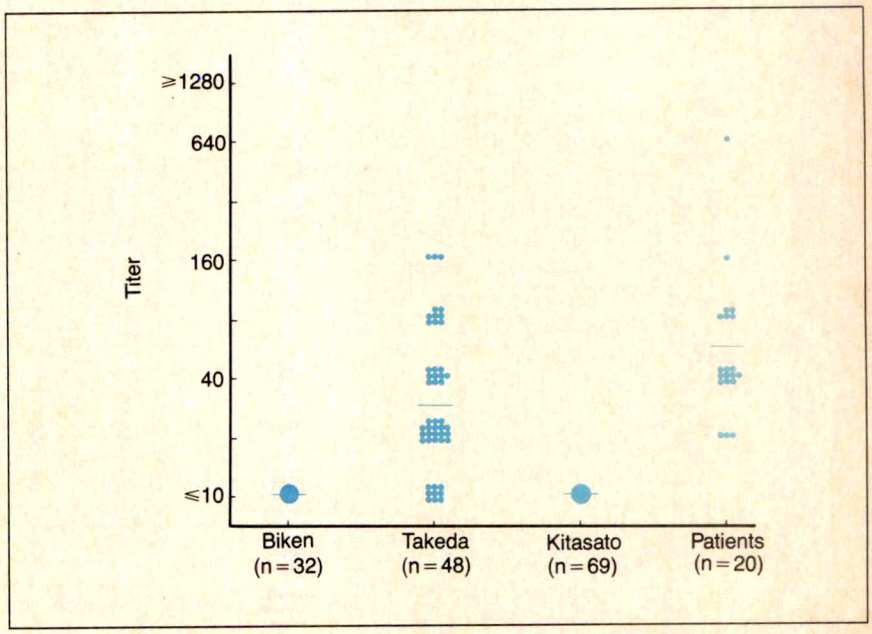


Fig 3.—Comparison of serotype 1.3 agglutinin titer in children given three primary doses of acellular diphtheria, tetanus, and pertussis vaccine from one of the three manufacturers at 4 weeks after the last of the primary series, and patients with pertussis in the convalescent stage. Bar indicates geometric mean.

Eighty-one children who received three primary doses of Kitasato lot 17 every 4 weeks were separated into four groups by age when the first dose was given: 18 children at the age of 3 to 6 months; 20 at the age of 7 to 11 months;

31 at the age of 12 to 23 months; and 12 at the age of 24 to 35 months (Fig 4). The geometric mean of prevaccination anti-PT and anti–F-HA antibody in the four groups were all less than 1 enzyme-linked immunosorbent assay unit/mL, and no difference in prevaccination anti-PT and anti–F-HA levels was present among the four groups. In anti-PT antibody levels 4 weeks after the third dose, there were no differences at all among the four age groups. Although anti–F-HA antibody levels in children aged 3 to 6 months were significantly lower than those aged 7 months or over ($P<.05$), the geometric mean of anti–F-HA antibody in children aged 3 to 6 months was still four times higher than that of patients with pertussis in the convalescent stage ($P<.01$).

Efficacy of Acellular Pertussis Vaccine

The survey of the 495 households identified 503 children who were household contacts, excluding 22 children who were coprimary cases. The secondary attack rate was 96 (89.7%) of 107 in unimmunized children aged 0 to 1 year and 47 (59.5%) of 79 in unimmunized children aged 2 to 8 years. In fully immunized children aged 2 to 8 years, the secondary attack rate was 11 (10.5%) of 105 for acellular pertussis vaccine, 7 (13.5%) of 52 for whole-cell vaccine, and 5 (13.5%) of 37 for those vaccinated with a combination of both acellular and whole-cell vaccine. The attack rate in unimmunized children aged 2 to 8 years was significantly higher than that in any fully immunized group ($P<.01$) (Table 3).

The secondary attack rates for acellular vaccines by manufacturer were 1 of 8 for Biken, 2 of 18 for Takeda, 1 of 17 for Kitasato, 2 of 13 for Chiba, 0 of 7 for Denka, and 0 of 2 for Kaketsu. Twenty-nine children were fully immunized with acellular DTP vaccines from two different manufacturers, and the attack rate was 3 of 29. The manufacturer of the acellular DTP vaccine could not be determined in 11 fully immunized children, and the attack rate was 2 of 11. There were no immunized children younger than 2 years old, which restricted the calculation of vaccine efficacy to children aged 2 to 8 years. The overall estimate was 82%, and the efficacy estimates for each manufacturer were 79.0% for Biken, 81.3% for Takeda, 90.1% for Kitasato, 74.1% for Chiba, and 100% for Denka. Efficacy was defined as follows: [(attack rate in unimmunized group − attack rate in immunized group)/attack rate in unimmunized group] × 100.

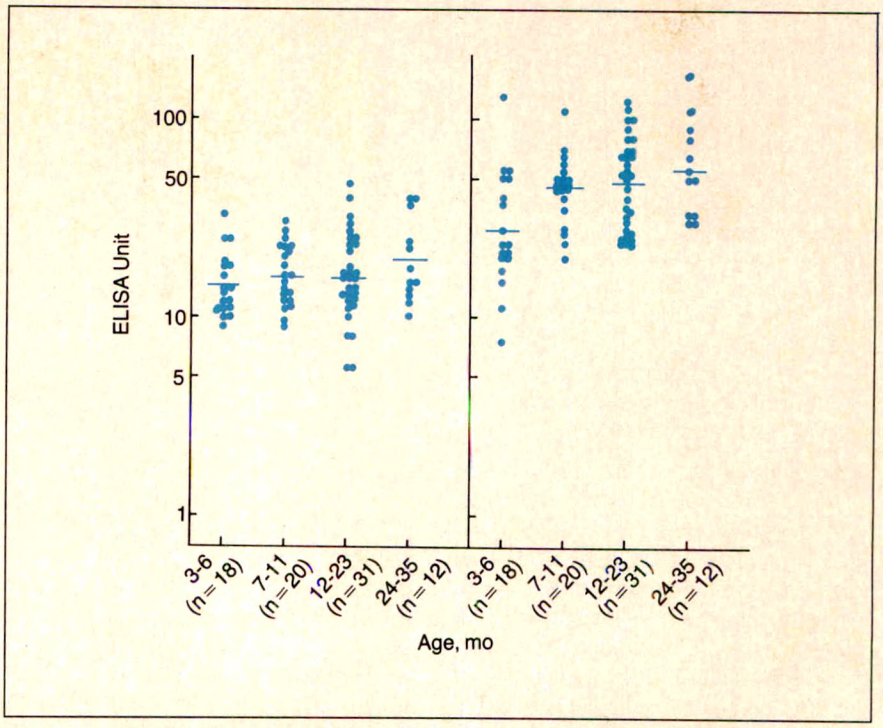


Fig 4.—Comparison of anti–pertussis toxin (left) and anti–filamentous hemagglutinin (right) antibody responses at 4 weeks after the third dose of acellular diphtheria, tetanus, and pertussis vaccine, Kitasato lot 17, by age when the first dose was given. The geometric mean (indicated by bar) of anti–pertussis toxin and anti–filamentous hemagglutinin antibody in prevaccination sera were less than 1 enzyme-linked immunosorbent assay (ELISA) unit/mL in the four groups. No difference in anti–pertussis toxin and anti–filamentous hemagglutinin antibody levels was present in the prevaccination sera among the four groups.

Table 3.—Secondary Attack Rate in Household Contacts by Age and Vaccination Status*

Age, y	Not Immunized	Fully Immunized			Partially Immunized		Previous Pertussis
		AC	WC	Both	AC	WC	
0-1	96/107	0	0	0	0	0	0
2-4	31/42	9/72	1/4	2/10	3/6	0	0
5-8	16/37	2/33	6/48	3/27	0/2	0/5	1/5
>9	3/11	0	11/83	0/4	0	3/4	0/3
2-8 (%)	**47/79** (59.5)	**11/105†** (10.5)	**7/52†** (13.5)	**5/37†** (13.5)	**3/8** ...	**0/5** ...	**1/5** ...

*AC indicates diphtheria, tetanus, pertussis containing acellular pertussis vaccine; WC, diphtheria, tetanus, pertussis containing whole-cell pertussis vaccine; and both, immunized partly with WC and partly with AC. Values are number with feature/total number.

†$P<.01$ compared with children aged 2 to 8 years who were not immunized.

COMMENT

We investigated the immunogenicity of acellular pertussis vaccine from three representative Japanese manufacturers, Biken, Takeda, and Kitasato. There were significant differences in anti-PT antibody, anti–F-HA antibody,

and agglutinin responses between the three manufacturers. As there is no universal index available for pertussis antibodies, the immunogenicity of acellular vaccine in children was compared with age-matched patients with pertussis in the convalescent stage. The anti-PT antibody level of children given the Biken vaccine was 2.5 times as high as that of the corresponding patients, and the anti-PT antibody level of children given Takeda and Kitasato vaccines was almost the same as that of patients with pertussis in the convalescent stage. The anti–F-HA antibody responses were much higher in the children who were administered vaccines from the three tested manufacturers than that in patients with pertussis. Agglutinin responses were absent in the children given Biken and Kitasato vaccines, and half as high in those given Takeda vaccine as that of patients. In spite of the significant differences, all of the children who took the three acellular DTP vaccines tested in this study produced both anti-PT antibody, which is at least comparable with patients with pertussis in the convalescent stage, and anti–F-HA antibody far higher than that of convalescing patients.

Pertussis toxin content of acellular DTP vaccine is 5 to 6 mg of protein nitrogen per liter in Biken and 1 to 2 mg of protein nitrogen per liter in Takeda and Kitasato vaccines. Filamentous hemagglutinin content of acellular DTP vaccine is 5 to 6 mg of protein nitrogen per liter in Biken and 10 to 12 mg of protein nitrogen per liter in Takeda and Kitasato vaccines. Acellular DTP vaccine of Takeda contains small amounts of agglutinogens. These data indicate that antigen content is a major determinant of resultant antibody responses in acellular DTP vaccine.

All efficacy data from Japan include children aged 2 years or over because this is the recommended age for initiation of mass DTP vaccination. Because of this lack of data for young children, the immunogenicity of Japanese acellular DTP vaccine by age was also investigated. The study proved that the immunogenicity of acellular DTP vaccine in children aged 3 to 6 months was not so different from that of children aged 2 years. We would therefore expect acellular DTP vaccine to be effective in children less than 2 years old as in older children.

Since proof of protection from the disease is the only acceptable measure of vaccine efficacy,[13] we have continued our household contact study of pertussis begun in 1981. We have accumulated 495 households and the calculated efficacy of Japanese acellular pertussis vaccine is 82% (95% confidence interval, 68% to 90%). A large-scale efficacy trial was conducted in Sweden with Japanese acellular pertussis vaccine, which was essentially the same as the acellular vaccine of Biken used in this study. The Swedish trial showed that acellular vaccine was 80% effective in the prevention of whooping cough of over 30 days' duration.[4] Our results were quite comparable with the Swedish trial, though these two trials are different in several methodological ways. Since the antigenic makeup of acellular vaccine is different by manufacturer, the vaccine efficacy by manufacturer also was calculated. Although the calculated efficacy ranged from 74% to 100% partly because of the small number of household contacts, every manufacturer appeared to be similarly effective.

Although the three tested manufacturers were very different in terms of their immunogenicity and antigen contents, the estimated efficacy in our survey was the same. It is assumed from these results that an effective vaccine needs to produce anti-PT antibody levels that are at least comparable with patients with pertussis in the convalescent stage. Filamentous hemagglutinin and agglutinogens might make acellular vaccines more effective, though it is still uncertain whether F-HA and agglutinogens are necessary for effective acellular vaccines. This is because F-HA and agglutinogens have been shown to be protective antigens in animal experiments,[14] and the Swedish trial suggested that a PT–F-HA two-component vaccine might be more effective in the prevention of pertussis than a PT-monovalent vaccine.[4]

Finally, we expect that continuing this household study will allow us to assess the efficacy of Japanese acellular pertussis vaccines more clearly. We hope that the introduction of this acellular vaccine in the near future will prevent the children of the world from acquiring pertussis and its associated morbidity and mortality.

We would like to thank Mitsuru Osano, MD, for advice; the staff of the vaccine research group in the Pediatric Department, Keio University, Tokyo, Japan; the pediatricians of Saiseikai Utsunomiya Hospital, Japan, and Azabu Nyujiin, Tokyo, for technical assistance; and Steven S. Salisbury, MD, of the US Air Force Hospital, Yokota, Japan, and M. Saito, MD, of the Pediatric Department, Keio University, for their help in the manuscript preparation; and the parents of patients with pertussis for providing valuable information.

References

1. *Precipitated-Purified Pertussis Vaccine: Minimum Requirement for Biological Products.* Tokyo, Japan: Ministry of Health and Welfare; 1982:129-139.

2. Sato Y, Kimura M, Fukumi H. Development of a pertussis component vaccine in Japan. *Lancet.* 1984;1:122-126.

3. Nobel GR, Bernier RH, Esber EC, et al. Acellular and whole-cell pertussis vaccines in Japan: report of a visit by US scientists. *JAMA.* 1987;257:1351-1356.

4. Ad Hoc Group for the Study of Pertussis Vaccines. Placebo-controlled trial of two acellular vaccines in Sweden: protective efficacy and adverse events. *Lancet.* 1988;1:955-960.

5. Hedenskog S, Granström M, Olin P, Tiru M, Sato Y. A clinical trial of a monocomponent pertussis toxoid vaccine. *AJDC.* 1987;141:844-847.

6. Lewis K, Cherry JD, Holroyd HJ, Baker LR, Dudenhoeffer FE, Robinson RG: A double-blind study comparing an acellular pertussis-component DTP vaccine with a whole-cell pertussis-component DTP vaccine in 18-month-old children. *AJDC.* 1986;140:872-876.

7. Edwards KM, Lawrence E, Wright PF. Diphtheria, tetanus, and pertussis vaccine: a comparison of the immune response and adverse reactions to conventional and acellular pertussis components. *AJDC.* 1986;140:867-871.

8. Anderson EL, Belshe RB, Bartram J. Differences in reactogenicity and antigenicity of acellular and standard pertussis vaccines combined with diphtheria and tetanus in infants. *J Infect Dis.* 1988;157:731-737.

9. Aoyama T, Murase Y, Kato T, Iwata T. Efficacy of an acellular pertussis vaccine in Japan. *J Pediatr.* 1985;107:180-183.

10. Aoyama T, Murase Y, Gonda T, Iwata T. Type-specific efficacy of acellular pertussis vaccine. *AJDC.* 1988;142:40-42.

11. Manclark CR, Meade BD. Serological response to *Bordetella pertussis.* In: Rose NR, Friedman H, eds. *Manual of Clinical Immunology.* 2nd ed. Washington, DC: American Society for Microbiology; 1980:496-499.

12. Aoyama T, Hagiwara S, Murase Y, Kato T, Iwata T. Adverse reactions and antibody responses to acellular pertussis vaccine. *J Pediatr.* 1986; 109:925-930.

13. Manclark CR. *Pertussis Vaccine Research.* New York, NY: World Health Organization; 1981;59:9-15.

14. Pittman M. The concept of pertussis as a toxin-mediated disease. *Pediatr Infect Dis J.* 1984;3:467-486.

Evaluation of the Vomiting Infant

L. Christopher Foley, MD; Thomas L. Slovis, MD; John B. Campbell, MD; John D. Strain, MD; Lee A. Harvey, MD; Dennis W. Luckey, PhD

• **This 12-month prospective study was undertaken to evaluate the cost, risk, and benefit of ultrasound followed by upper gastrointestinal series for the evaluation of the infant who vomits. Results suggest minimal morbidity from the upper gastrointestinal series, only a 33% reduction in the number of upper gastrointestinal series performed, and a 95% increase in cost if this imaging sequence is used. We conclude that the use of ultrasound for the initial evaluation of vomiting in infants substantially increases the cost with no meaningful decrease in morbidity and mortality.**

(*AJDC*. 1989;143:660-661)

Current literature suggests that ultrasound be used as the initial imaging approach to the infant who vomits. Traditional upper gastrointestinal (UGI) series is then performed only in those patients without evidence of hypertrophic pyloric stenosis (HPS) by ultrasound criteria.[1-4] Proponents justify this change by a decrease in radiation dose and a decrease in the risk of aspiration without sacrificing diagnostic accuracy. However, if the prevalence of HPS and the morbidity of UGI in this population is sufficiently low, this change may not be justified. This collaborative study from The Children's Hospital of Michigan, Detroit, and The Children's Hospital in Denver, Colo, was undertaken to assess this imaging approach.

PATIENTS AND METHODS

All patients between the ages of 1 and 8 weeks presenting to the radiology department of both institutions from May 1, 1985, to April 30, 1986, for the complaint of recurrent vomiting were prospectively evaluated using the UGI series. Patients with important findings other than vomiting, including bilious emesis or hematemesis, were excluded from this study. The radiologic diagnosis was listed when the examination was performed. Surgical confirmation of the diagnosis, if available, was obtained. Average cost of the UGI series and ultrasound at both institutions, including both professional and performance fees, was determined.

RESULTS

A total of 112 patients between the ages of 1 and 8 weeks were evaluated for vomiting using the UGI series, 56 from each institution. Thirty-seven (33%) of these patients were proved to have HPS. Forty-six patients (41%) had gastroesophageal reflux without another abnormality. Thirteen patients (12%) were identified with abnormalities other than gastroesophageal reflux or HPS (namely, antral spasm, 5 [4%]; malrotation, 4 [4%]; and 1 each [1%] with hiatus hernia, gastritis-ulcer, pharyngeal tear, and swallowing dysfunction). Sixteen patients (14%) had normal examination findings.

COMMENT

There is little doubt that both ultrasound and the UGI series will identify the patient with HPS.[1-10] In our series, 67% of all patients had a cause of vomiting other than HPS. Twelve percent of these patients had abnormalities other than HPS or gastroesophageal reflux. Certainly, some causes of vomiting other than HPS can be identified by ultrasound.[11] However, the confidence level for the presence or, more importantly, the absence of these abnormalities will likely remain low for most examiners.[2] For that reason, most authors who prefer ultrasound as the initial imaging modality suggest that evaluation using the UGI series is appropriate if HPS is not identified as the cause of vomiting. If ultrasound replaces the UGI series as the initial imaging study and the UGI series is not performed, the cost of imaging will increase if ultrasound is more expensive. This is true in our institutions where the average charge for an UGI series is $173 for the professional and performance component and the average charge for ultrasound is $221. This translates to a 28% increase in cost. If the UGI series is performed on all of the infants without ultrasonographic evidence of HPS, the cost will be increased by the number of studies performed. If the prevalence of HPS is 33% as in this series, there will be a 67% additional cost for the UGI series. The total increase in cost is then 95%. If residual barium in the stomach from the UGI series delays operative intervention, or if complications from the UGI series increase the hospital stay, the overall cost may increase. Consequently, all patients of all ages with an operative diagnosis of HPS at The Children's Hospital, Denver, during the same 1-year period as above were identified retrospectively, and the length of the hospital stay was determined. In the 29 patients identified, the average length of stay for the patients not having UGI was 3 days and for patients having the UGI series was 2.8 days. Apparently then, there is no increase in hospital stay when the UGI series is utilized.

This cost increase may be necessary if ultrasound reduces patient morbidity. Certainly ultrasound decreases radiation dose. The risk of cancer induction due to small x-ray doses is subject to some question. In the absence of any increased radiation exposure, the incidence of cancer death is about 164 000 per 1 million persons,[12] an individual risk of 0.164. A realistic assumption of radiation risk is 1 excess cancer death in 10 000 persons each receiving 0.01 Gy of whole-body irradiation,[13] a minimal in-

Accepted for publication January 19, 1989.

From the Divisions of Radiology (Drs Foley, Campbell, Strain, and Harvey) and Pathology (Dr Luckey), The Children's Hospital, Denver, Colo; and the Division of Radiology, Children's Hospital of Michigan, Detroit (Dr Slovis).

Reprint requests to 1056 E 19th Ave, Denver, CO 80218 (Dr Foley).

crease of little real importance in diagnostic imaging.[4]

Aspiration of barium during the UGI series is also of concern.[14] All children face the risk of pulmonary complications and death from aspiration of gastric content. This risk is equal to the probability that a child will vomit times the probability that a child will aspirate times the probability that aspiration will have a morbid outcome. The UGI series may increase vomiting to the extent that any feeding may increase vomiting. If the UGI series is performed properly with the patient right side down or prone, and the volume of contrast material does not exceed a normal feeding, neither the risk of aspiration nor the volume of aspirate will increase should vomiting occur. Because barium is no more toxic than gastric acid or milk,[15-17] the contrast agent does not increase the risk of morbid outcome should aspiration occur. Consequently, the risk of aspiration during the UGI series is the same as the risk of aspiration during any feeding. The magnitude of the aspiration risk of one feeding is not quantified. However, the incidence of death due to aspiration of gastric content can be estimated at 3 per 100 000 in infants younger than 1 year of age, including those with neurologic and swallowing defects.[18] Because vomiting is common, the incidence of aspiration death following any single episode of emesis regardless of cause should be no greater than this small risk and because every feeding is not followed by vomiting, the risk of a single feeding should be even less.

CONCLUSION

The use of the UGI series alone for evaluating the infant who vomits poses risks from aspiration and irradiation that are vanishingly small. The use of ultrasound alone eliminates these risks with the possibility of a 12% rate of misdiagnosis and a potential increase in cost of 28%. The use of ultrasound with two thirds of the infants requiring the UGI series to eliminate this potential false-negative rate decreases the already minimal morbidity and mortality by 33% but may increase the cost by 95%. We conclude that the use of ultrasound for the initial evaluation of vomiting in infants substantially increases the cost of diagnosis with no meaningful decrease in morbidity or mortality.

References

1. Haller JO, Cohen HL. Hypertrophic pyloric stenosis: diagnosis using US. *Radiology.* 1986;161:335-339.
2. Blumhagen JD. The role of ultrasonography in the evaluation of vomiting in infants. *Pediatr Radiol.* 1986;16:267-270.
3. Stunden RJ, LeQuesne GW, Little KET. The improved ultrasound diagnosis of hypertrophic pyloric stenosis. *Pediatr Radiol.* 1986;16:200-205.
4. Leonidas JC. Decision-making in pediatric radiology: the case of hypertrophic pyloric stenosis. *Diagn Imaging Clin Med.* March 1986:75-81.
5. Blumhagen JD, Noble HGS. Muscle thickness in hypertrophic pyloric stenosis: sonographic determination. *AJR.* 1983;140:221-223.
6. Wilson DS, Vanhoutte JJ. The reliable sonographic diagnosis of hypertrophic pyloric stenosis. *JCU.* 1984;12:201-204.
7. Strauss S, Itzchak Y, Manor A, Heyman Z, Graif M. Sonography of hypertrophic pyloric stenosis. *AJR.* 1981;136:1057-1058.
8. Khamapirad T, Athey PA. Ultrasound diagnosis of hypertrophic pyloric stenosis. *J Pediatr.* 1983;102:23-26.
9. Ball TI, Atkinson GO, Gay BB. Ultrasound diagnosis of hypertrophic pyloric stenosis: real-time application and the demonstration of a new sonographic sign. *Radiology.* 1983;147:499-502.
10. Yip WCL, Tay JSH, Wong HB. Sonographic diagnosis of infantile hypertrophic pyloric stenosis: critical appraisal of reliability and diagnostic criteria. *JCU.* 1985;13:329-332.
11. Hayden CK, Boulden TF, Swischuk LE, Lobe TE. Sonographic demonstration of duodenal obstruction with midgut volvulus. *AJR.* 1984;143:9-10.
12. Fabrikant JI. The BEIR III report: origin of the controversy. *AJR.* 1981;136:209-214.
13. Webster EW. On the question of cancer induction by small x-ray doses. *AJR.* 1981;137:647-666.
14. McAlister WH, Siegel MJ. Fatal aspirations in infancy during gastrointestinal series. *Pediatr Radiol.* 1984;14:81-83.
15. McAlister WH, Askin FB. The effect of some contrast agents in the lung: an experimental study in the rat and dog. *AJR.* 1983;140:245-251.
16. Moran TJ. Milk-aspiration pneumonia in human and animal subjects. *Arch Pathol Lab Med.* 1952;55:286-301.
17. Bynum LJ, Pierce AK. Pulmonary aspiration of gastric contents. *Am Rev Respir Dis.* 1976;114:1129-1135.
18. Harris CS, Baker SP, Smith GA, Harris RM. Childhood asphyxiation by food: a national analysis and overview. *JAMA.* 1984;251:2231-2235.

In Other AMA Journals

ARCHIVES OF GENERAL PSYCHIATRY

A Controlled Family History Study of Prepubertal Major Depressive Disorder

Joachim Puig-Antich, MD; Deborah Goetz; Mark Davies, MPH; Thelma Kaplan, MS; Sharon Davies, RN; Lynn Ostrow, RN, MA; Lauren Asnis; Janet Twomey; Satish Iyengar, PhD; Neal D. Ryan, MD (*Arch Gen Psychiatry.* 1989;46:406-418)

The Effect of Respiratory Viral Infections on Patients With Cystic Fibrosis

Bonnie W. Ramsey, MD; Edmond J. Gore, PhD; Arnold L. Smith, MD; Marion K. Cooney, PhD†; Gregory J. Redding, MD; Hjordis Foy, MD

• We examined, in a 2-year prospective study, the frequency of respiratory viral infections in 19 school-age patients with cystic fibrosis and their unaffected siblings. At 2-month intervals throughout the study period, pulmonary function tests, oropharyngeal cultures, and serologic tests for respiratory viruses were performed in all subjects. Quantitative sputum cultures for bacteria were performed in subjects with cystic fibrosis. The same laboratory specimens were also collected at the time of all acute respiratory illnesses. Over the 2-year period, 398 viral cultures and serum samples were collected, 210 from patients with cystic fibrosis and 188 from their siblings. The frequency of culture-documented and seropositive viral infections was not significantly different between patients with cystic fibrosis and their siblings. The patients with the highest frequency of viral infection were younger and had the lowest rate of decline in lung function and severity score. We conclude that school-age patients with cystic fibrosis are no more susceptible to viral infections than their unaffected siblings. We were unable to demonstrate any significant adverse effect of respiratory viral infections on pulmonary function in 19 patients with cystic fibrosis aged 5 to 21 years.

(*AJDC*. 1989;143:662-668)

Progressive obstructive lung disease is the cause of death in 95% of children with cystic fibrosis (CF).[1] Although the endobronchial tree in patients with CF consistently yields *Staphylococcus aureus* and *Pseudomonas aeruginosa*, appropriate antibiotic therapy has had a limited effect in slowing the progression of lung disease.[2] For this reason, others have hypothesized that additional factors, such as altered immune function[3,4] and respiratory viral infections,[5] may be contributing to airway destruction.

Respiratory viruses and *Mycoplasma pneumoniae* are the most common causes of lower respiratory tract infections in children.[6,7] Studies of adults with chronic obstructive pulmonary disease[8-16] and children with asthma[17] have demonstrated a significant increase in pulmonary symptoms at the time of respiratory viral infections. Furthermore, patients with CF hospitalized for pulmonary exacerbations have respiratory viruses isolated from the respiratory tract.[18]

In spite of the potential importance of respiratory viruses in CF, few prospective studies[19-22] have been reported. Most studies have been hampered by a limited use of control subjects, the lack of viral isolation, and the failure to use objective indicators, such as pulmonary function tests, to define pulmonary infection. Workers in Toronto, Canada,[22] studied patients and controls for more than one respiratory season and found that patients with CF reported a higher number of symptomatic respiratory illnesses than their unaffected siblings, despite the same incidence of viral seroconversion in both groups. In addition, the rate of seroconversion was the same in patients with CF with and without respiratory symptoms. The finding of most concern in that study[22] was a significant correlation between decline in pulmonary function over the 2 years and the annual incidence of viral seroconversion.

In the present prospective study, we sought to determine whether patients with CF had an increased incidence of viral and *Mycoplasma* respiratory infection in comparison with a control group comprised of unaffected siblings. In addition, the cumulative effect of multiple viral infections on pulmonary function and clinical score was analyzed over the 2-year study period.

METHODS

Subject Contact

Nineteen sibling pairs consisting of one child with CF and one unaffected sibling were followed at Children's Hospital and Medical Center, Seattle, Wash, between July 1982 and June 1984. Prior to enrollment, informed consent was obtained from all study subjects and their legal guardians. The study was approved by the Children's Hospital and Medical Center institutional review board. All study subjects had a sweat chloride concentration determined by quantitative pilocarpine iontophoresis. All subjects with CF had sweat chloride concentrations equal to or greater than 80 mmol/L; siblings had a value less than 50 mmol/L. All subjects were required to perform reproducible pulmonary function tests necessitating a minimum enrollment age of 5 years. The enrollment age ranged from 5 to 22 years.

Sibling pairs were seen every 2 months when asymptomatic (defined as a "well" visit). Subjects and their parents were instructed to contact the research nurse or principal investigator at the onset of an acute respiratory illness (ARI). The presence of an ARI was defined using standardized criteria (Table 1). These criteria were given to each family for reference. Both siblings and subjects with CF were examined and cultured within 48 hours of the onset of an ARI. Parents of the sibling pairs were requested to record on a calendar the duration of ARIs. The research nurse contacted the subjects at 4-week intervals to increase compliance and completion of the illness calendars.

At each visit the following vital signs and anthropomorphic measurements were re-

Accepted for publication January 31, 1989.

From the Departments of Pediatrics (Drs Ramsey, Gore, Smith, and Redding), Pathobiology (Dr Cooney), and Epidemiology (Dr Foy), University of Washington, School of Medicine, Public Health and Community Medicine, Seattle, Wash.

†Deceased.

Reprint requests to Children's Hospital and Medical Center, PO Box C-5371, 4800 Sandpoint Way NE, Seattle, WA 98105 (Dr Ramsey).

Table 1.—Criteria Used to Define the Presence of an Acute Respiratory Illness (ARI) for Patients With Cystic Fibrosis (CF) and Unaffected Siblings*

1. New onset of runny nose or congestion
2. Temperature ≥38°C by mouth in previous 24 h
3. New onset of cough or sputum production (healthy sibling); increased frequency and duration of cough (child with CF)
4. New onset of sore throat
5. Myalgia and fatigue
6. Loss of appetite
7. School or work absenteeism because of respiratory symptoms
8. Sputum production increased by >50% in previous 24 h (patients with CF only)

*Sibling had ARI if four of seven criteria were present. Patient with CF had ARI if five of eight criteria were present.

corded on all subjects: temperature (in degrees centigrade), respiratory rate, pulse, height (in centimeters), weight (in kilograms), arm muscle circumference (in centimeters), and triceps fatfold thickness (in millimeters). A Shwachman-Kulczycki[23] illness severity score was recorded for each subject with CF. An oropharyngeal swab was obtained and cultured for respiratory viruses, and blood was obtained for determination of antibody titers against respiratory viruses and *M pneumoniae*. Subjects with CF expectorated sputum for quantitative bacterial culture.

During the study period, no subjects were prescribed prophylactic oral antibiotics. The principal investigator spoke with each subject's primary physician and requested that no antibiotics be prescribed without knowledge of the research team. To verify that the subjects with CF had not received additional antibiotic or other therapy for ARIs without the investigator's knowledge, the investigator reviewed each patient's medical record at the primary care physician's office.

At the time of an ARI visit, subjects with CF with *S aureus* colonization and a decrease in forced vital capacity (FVC) of at least 10% were administered cephalexin monohydrate by mouth for 10 days. Those subjects with CF with a predominance of *P aeruginosa* in their sputum and a decrease in FVC of at least 10% were admitted for 14 days of intravenous antipseudomonal antibiotic therapy.

Pulmonary Function Tests

Pulmonary function tests were performed by the same technician for the duration of the study. On recruitment into the study, subjects had two training sessions prior to the initiation of data collection. Throughout the study, the highest value measured at each testing session was recorded. Patients with CF performed pulmonary function tests at every visit, while siblings only performed the tests every 4 months for well visits, and at the time of each ARI (sick visit).

Lung volumes, flow rate, and airway resistance were measured by a flow displacement body plethysmograph (SRL 8000, Scientific Research Laboratories, Dayton, Ohio) and a No. 4 Fleisch pneumotachograph (Hans-Rudolph, Kansas City, Mo) using standardized techniques.[24] To allow for comparison of measurements over the 2-year study period when height and lung growth occurred, measurements were recorded in absolute units, but were expressed as the percent predicted for height.[25,26] Specific pulmonary functions measured were FVC, forced expiratory volume at 1 second, and forced expiratory flow, mid–expiratory phase ($FEF_{25\%-75\%}$). Calculated values included total lung capacity (TLC), residual volume (RV), and RV/TLC ratio. Abnormal volumes were defined as those not within 2 SDs of predicted values, based on height.[25,26]

Viral Isolation

Specimens were collected with a cotton-tipped swab from the posterior oropharynx, placed in 3 mL of trypticase soy broth with 0.5% bovine albumin, and frozen immediately at −70°C. After storage for 2 months, the specimens were thawed and inoculated into (1) Madin-Darby canine kidney cells with trypsin for isolation of influenza and parainfluenza viruses; (2) diploid line of fetal tonsil cells for isolation of rhinovirus, herpes group viruses, adenovirus, and picornavirus (except coxsackie B); and (3) HeLa cells susceptible to adenoviruses and coxsackie B viruses. During periods of increased respiratory syncytial virus activity, a fetal esophageal epithelial cell line was also inoculated. HeLa cells were incubated at 37°C for 1 week and blind-passed if no cytopathic effect was noted by 7 days. Madin-Darby canine kidney and fetal tonsil cells were incubated for 14 days at 34°C and examined microscopically at 2-day intervals for cytopathic effect. Madin-Darby canine kidney cells were tested for hemadsorption at 4-day intervals with guinea pig erythrocytes.[27] Cultures with hemadsorption activity or cytopathic effect were passed to fresh cells to confirm the presence of virus. The specific agent was then identified by hemadsorption inhibition or neutralization with type-specific antisera. Rhinovirus isolates were identified by acid sensitivity and cytopathic effect in fetal tonsil cells, but were not type identified.

Serologic Studies

Blood samples were assayed for antibody against respiratory viruses and *M pneumonia* using microtiter plates.[28] Serum controls, complement, antigen, and known reactive controls were included with each assay. The antigens tested were influenza A and B; parainfluenza 1, 2, and 3; adenovirus; respiratory syncytial virus; and *M pneumoniae*. Titers were expressed as the reciprocal of the highest dilution of serum that completely fixed complement. Serologic evidence of a viral or *Mycoplasma* infection was defined as a fourfold or greater increase in titer between paired serum samples collected at least 2 weeks apart. Seroconversion associated with an ARI was defined as a fourfold rise in antibody titer between paired serum samples; the first serum sample was collected at the time of the sick (ARI) visit and the second serum sample was collected 2 to 6 weeks later.

Seven patients with CF received H_3N_2 influenza vaccine in the fall of 1982 and 11 patients with CF received H_1N_1 in the fall of 1983. Paired serum samples from these patients were collected prior to vaccination and 2 to 6 weeks later and tested for hemagglutination inhibition response to influenza A and B, as well as complement fixation to determine whether an antibody response to the vaccine had occurred.

Bacteriologic Studies

Freshly expectorated sputum was collected by the research nurse and transported immediately to the Research Infectious Disease Laboratory at Children's Hospital and Medical Center. Sputum bacterial density (quantitative culture) was estimated by the method of Wong et al.[29] All organisms isolated from the sputum in densities equal to or greater than 10 000 colony-forming units (CFUs)/g were identified using standard techniques.[30]

Statistical Methods

Data analysis was performed using the Statistical Package for the Social Sciences. The χ^2 statistic was used to analyze categorical dependent variables such as patient sex. One-way and two-way ANOVAs were used to examine the relationships between independent variables (ie, patient gender) and continuous dependent variables (ie, frequency of viral infections per visit). An α (significance level) of 0.05 was used.

Linear regression analysis[31] was used to describe the trends of several study parameters for each patient in the group with CF over the 2-year study period. The regression equation expresses a study parameter as a weighted function of time. The weights provided a direct measure of the rate of change over time that was independent of variations in number of visits, length of time in the study, or clinical condition, thus controlling for differences among the subjects. Comparisons of β weights (representing change per study month) were made for patients with

differences in frequency of viral infections by use of ANOVA, for which age was controlled.

RESULTS

Patient Characteristics

Nineteen subjects with CF and their unaffected siblings were enrolled in the study in July 1982 and 15 completed the study in June 1984. Two patients (a 23-year-old man and an 18-year-old woman) died during the first year of the study and their siblings withdrew from the study. Two additional sibling pairs withdrew after moving. Analysis of the data was performed with and without these individuals and there were no significant differences. The mean enrollment age of the subjects with CF was 13.4±5.0 years and siblings was 13.4±3.4 years. The largest age span between siblings was 4 years. There were 10 male patients with CF and 6 female patients with CF, compared with 6 male siblings and 10 female siblings on enrollment. All sibling pairs lived in the same household and within 50 miles of Children's Hospital. All subjects regularly attended school or worked; none were homebound.

The siblings had normal pulmonary function at enrollment with a group mean FVC (percent predicted for height) of 102.0%±14.0%. In contrast, the mean FVC of patients with CF (percent predicted for height) at enrollment was lower: 72.7%±23.7%. The enrollment Shwachman-Kulczycki scores for subjects with CF ranged from 95 to 42, with a mean value of 69.5±17.0. At enrollment, endobronchial secretions of the 19 patients with CF contained the following bacterial pathogens: 8 with *S aureus*, 6 with both *S aureus* and *P aeruginosa*, 2 with *P aeruginosa* alone, and 3 had no pathogens isolated at a density of greater than 100 CFUs/g. For all subjects colonized with both *S aureus* and *P aeruginosa*, one bacteria was present in a much higher density, measured in colony-forming units per gram of sputum. This bacteria was defined as the predominant pathogen and accounted for at least 99% of the bacterial colonies.

Table 2.—Respiratory Illnesses and Infections in Patients With Cystic Fibrosis (CF) and Unaffected Siblings*

Clinical Variable	Subject Group		ANOVA†	
	Patient With CF	Sibling (n=19)	F	P
Respiratory illness,‡ d/y	22.5±21.1	7.8±8.8	7.89	.008
Oral antibiotics, d/y	73.9±96.4	2.2±7.2	10.47	.003
Intravenous antibiotics, d/y	29.8±48.2	0.0±0.0	7.25	.01
Viral isolates per visit	0.06±0.07	0.09±0.10	1.23	NS
Viral seroconversion per visit	0.14±0.13§	0.14±0.12	0.00	NS
Mycoplasma seroconversion per visit	0.03±0.05	0.05±0.07	1.01	NS
Total respiratory infection per visit‖	0.23±0.16	0.28±0.18	0.80	NS

*Data are expressed as mean±SD. NS indicates not significant.
†$df = 1,36$.
‡See Table 1 for definition.
§Rate excludes seven patients with serologic titer rise against influenza A following influenza vaccination.
‖Includes all study visits with a positive isolate and/or seroconversion.

Respiratory Symptoms

During the study period, the patients with CF had 210 visits compared with 188 visits for the sibling group. A significantly greater portion of visits from patients with CF (32.4%) than sibling visits (10.6%) were for ARI symptoms ($\chi^2 = 27.17$, $df = 1$; $P < .001$). As is shown in Table 2, the patients with CF recorded significantly more days with ARI symptoms per year than did the sibling group. As expected, the patients with CF had a greater number of days per year receiving oral and/or intravenous antibiotics than their siblings.

Viral and *Mycoplasma* Infections

From the 398 viral cultures and serum samples collected over the 2-year period, 30 viral isolates, 68 seroconversions against respiratory viruses, and 14 seroconversions against *M pneumoniae* were identified. The viral isolation rate for all subjects was 7.5%, which was comparable with the rate of 6.3% obtained as part of a concurrent respiratory disease surveillance study[32] performed in the Seattle area. The seroconversion rate against respiratory pathogens was 19.8% for all subjects. The viral isolation rate, the viral and *Mycoplasma* seroconversion rate, and total respiratory infection rate were slightly higher among siblings than patients with CF. However, none of these differences were statistically significant (Table 2). Neither group had evidence of chronic oropharyngeal colonization with a respiratory viral pathogen. The frequency of isolating a respiratory virus at the time of ARI was 8.8% for subjects with CF and 15.0% for siblings in comparison with a frequency of 5.6% for subjects with CF and 7.7% for siblings when they were asymptomatic. The frequency of seroconversion following ARI was 19.1% for the patients with CF and 15.0% for the siblings, compared with 16.2% of the patients with CF and 20.2% of the siblings when well. By χ^2 analysis, none of these frequencies were significantly different between ARI and well visits.

The viral and *Mycoplasma* agents identified during the study are listed in Table 3. Respiratory syncytial virus, adenovirus, and parainfluenza virus infection were identified by serologic testing but were not isolated from any study subjects. The group of patients with CF appeared to have a greater frequency of isolation of rhinoviruses and a higher seroconversion rate against parainfluenza viruses than their siblings; however, these differences were not significant. Six subjects with CF and eight siblings had a seroconversion to *M pneumoniae*. Thirty-four percent of all the infections were common to the same household, ie, infection by the same pathogen in both members of the sibling pair within an 8-week period. Patients

Table 3.—Viral and *Mycoplasma* Pathogens Identified by Isolation and/or Seroconversion in Patients With Cystic Fibrosis (CF) and Unaffected Siblings

Respiratory Agents	Patients With CF		Siblings		Concomitant Infection*
	Viral Isolate	Seroconversion	Viral Isolate	Seroconversion	
Respiratory syncytial virus	0	9	0	11	6
Adenovirus	0	3	0	2	2
Parainfluenza 1, 2, 3	0	12	0	7	4
Influenza A	1	2 (9)†	2‡	6‡	4
Influenza B	0	3	1§	7§	2
Rhinovirus	11	...	5	...	6
Mycoplasma pneumoniae	...	6	...	8	8
Enterovirus	1	...	5	...	0
Herpes simplex	1	...	3	...	2
Subtotal	**14**	**35 (42)†**	**16**	**41**	**34**
Total infections		49		54	34

*Concomitant infection was defined as the same type of respiratory infection in both members of a sibling pair within an 8-week period.

†An additional seven patients with CF demonstrated an increase in serologic titer following influenza vaccine.

‡One sibling demonstrated a seroconversion against influenza A 1 month after isolation of the virus.

§One sibling demonstrated a concomitant serologic rise against influenza B and isolation of the virus.

with CF and siblings were equally likely to have the initial infection within the household.

Seven patients with CF received H_3N_2 influenza vaccine in the fall of 1982, and 11 patients with CF received the H_1N_1 vaccine in the fall of 1983. None of the siblings received vaccinations. These were "split-virus vaccines" with exposed viral nucleoprotein and M protein antigen, which elicit a complement fixation antibody response[33] as well as hemagglutination inhibition response.

All patients had significant (≥1:80) hemagglutination inhibition response titers against influenza A prior to vaccination; only one patient demonstrated a fourfold increase in antibody titer. By complement fixation, however, there was evidence of response against influenza A in 7 of 18 vaccinations. Hemagglutination inhibition response titers demonstrated a rise to influenza B in 4 of 18 vaccinations.

During the study period, the sibling group had 14 influenza infections identified (7 influenza A and 7 influenza B), an infection rate per visit of 7.8%. The group of patients with CF had six natural infections identified (three influenza A and three influenza B) with a rate per visit of 2.8%. Of these infections, three were in patients with CF recently vaccinated (≤6 months prior) and three were patients who had not been vaccinated during the study period. It should be noted, however, that "nonvaccinated" patients also had elevated hemagglutination inhibition response titers against influenza A (≥1:80). Of the 14 sibling influenza infections, 3 were transmitted to the child with CF in the household (a secondary attack rate of 21%). Two of these patients with CF had been vaccinated within the previous 6 months. The secondary attack rate for influenza within a family has been reported to be 27%.[34]

Effect of Disease Severity on the Viral and *Mycoplasma* Infection Rate in CF

The effects of age, gender, and illness severity on the frequency of viral and *Mycoplasma* infection in subjects with CF were analyzed. Pearson correlation coefficients were derived to quantify the relationship of three continuous variables—age, FVC, and Shwachman-Kulczycki clinical score—to the frequency of infection. The two categorical variables, gender and predominant bacterial pathogen (≥10^6 CFUs/g), were analyzed by ANOVA. There was a significant correlation of age with infection rate ($r = -.50$; $P < .05$), ie, the younger patients with CF had more viral and *Mycoplasma* infections per visit than older patients with CF. Two measures of illness severity, FVC and Shwachman-Kulczycki score, did not significantly correlate with infection rate. Patient gender did not affect the rate of infection. There was a significant difference in the frequency of viral infection between subjects with CF colonized predominantly with *S aureus* and those with predominantly *P aeruginosa* ($F[1,14] = 9.09$; $P < .01$). The mean number of viral and *Mycoplasma* infections per visit was higher for patients with CF who had a predominance of *S aureus* (0.30 ± 0.15) than patients with CF who had a predominance of *P aeruginosa* (0.10 ± 0.05). This difference remained significant after controlling for the effect of age. The infection rate for the subjects with CF colonized with *S aureus* was similar to the unaffected siblings (0.28 ± 0.18). The infection rate for the *P aeruginosa*–colonized subjects with CF was significantly lower ($P < .01$).

Clinical Response of Subjects With CF to Viral Infections

To understand the relationship between respiratory viral infections and clinical response in subjects with CF, measurements of pulmonary function (FVC, $FEF_{25\%-75\%}$, and RV/TLC ratio), temperature, pulse, respiratory rate, and white blood cell count were compared in the absence and presence of documented infections. At study initiation, it was hypothesized that most respiratory viruses would be identified at the time of a sick (ARI) visit. Only one third of the infections, however, were identified during an ARI, and the association of ARI and viral infections was not significant by χ^2 analysis, ($\chi^2 = 0.3$, $df = 1$; $P = .4$). For this reason, it was necessary to analyze the effect of ARI and viral infections separately. Two-way ANOVAs were performed to determine whether the effects of respiratory viral infections and ARI were additive or interactive (Table 4). For all

Table 4.—Comparison of Patients With Cystic Fibrosis (CF) in the Absence and Presence of Both Acute Respiratory Illness (ARI) and Viral Infections for Physical and Laboratory Measures*

Clinical Variable	ARI Absent		ARI Present		ANOVA,† Subject × Virus
	Virus Absent	Virus Present	Virus Absent	Virus Present	
Physical variables					
Temperature, °C	36.80 ± 0.44	36.75 ± 0.40	37.12 ± 0.83	37.12 ± 0.58	F = 0.07; NS
Respirations/min	94.4 ± 14.5	90.1 ± 13.9	102.0 ± 17.7	100.0 ± 12.8	F = 0.55; NS
Respiratory rate, breaths per minute	27.8 ± 6.3	25.6 ± 7.6	31.1 ± 7.7	32.6 ± 6.3	F = 4.38; $P = .04$
No. of visits	111	31	49	19	. . .
Laboratory measures					
White blood cell count, $\times 10^9$/L	12.1 ± 4.3	10.5 ± 3.4	12.3 ± 3.8	12.9 ± 4.1	F = 2.34; NS
FVC, % predicted	70.3 ± 18.3	86.4 ± 20.2	66.2 ± 21.4	59.2 ± 16.7	F = 10.66; $P < .001$
$FEF_{25\%-75\%}$, % predicted	28.1 ± 16.0	44.7 ± 29.8	22.5 ± 15.7	19.3 ± 8.8	F = 7.93; $P = .005$
RV/TLC, %	50.2 ± 12.8	44.7 ± 10.3	53.6 ± 13.8	58.3 ± 14.6	F = 5.31; $P = .02$
No. of visits‡	109	31	46	16	. . .

*Data are expressed as mean ± SD. FVC indicates forced vital capacity; $FEF_{25\%-75\%}$, forced expiratory flow, mid–expiratory phase; RV, residual volume; TLC, total lung capacity; and NS, not significant.
†$df = 1, 205$ for the physical measures and 1, 197 for the laboratory measures.
‡Laboratory measures could not be completed for eight visits by patients with CF.

the analyses, the effects of age were controlled.

As seen in Table 4, subjects who were symptomatic at the time of a viral infection had the highest respiratory rate, most air trapping (RV/TLC ratio), and lowest measures of FVC and $FEF_{25\%-75\%}$. All measures were consistent with significant airway obstruction. In contrast, asymptomatic subjects with CF who had viral infection demonstrated the best pulmonary function measures and lowest respiratory rate.

The unexpected improvement in lung function with viral infection (without ARI) could have been due to the time lag between viral infections and serologic response. We explored this possibility by examining only those viral infections diagnosed by viral isolation. While there were only eight such infections, precluding reliable statistical comparison, the increase in FVC and $FEF_{25\%-75\%}$ and the decrease in RV/TLC ratio for subjects with CF were still apparent. For subjects with CF (without ARI) the mean FVC (percent predicted for height) was 70.3% ± 18.3% without and 91.8% ± 29.6% with a viral isolate; the mean $FEF_{25\%-75\%}$ (percent predicted) was 28.1% ± 16.0% without and 59.3% ± 41.1% with viral isolate; and the mean RV/TLC ratio was 50.0% ± 12.8% without and 47.9% ± 14.1% with a viral isolate.

Effect of Respiratory Viral Infections on Progression of Pulmonary Disease in Patients With CF

To identify a potential cumulative effect of viral infections on the progression of CF pulmonary disease over the 2-year study period, trends in several clinical indexes were assessed by linear regression. The indexes analyzed were FVC, RV/TLC ratio, Shwachman-Kulczycki score, respiratory rate, arm muscle circumference and triceps fat-fold thickness. Regression slopes (β weights) were obtained for each subject with CF. Because 2 years of measurements were necessary to obtain stable estimates of disease progression, the four patients who did not complete the study were omitted from the regression analysis.

Analysis of variance was used to compare the regression slopes of those study members with CF with high (one or more infections in five visits) and low (less than one infection in five visits) frequency of viral and *Mycoplasma* infections (Table 4). The frequency cutoff between groups (one infection in five visits) was the mean value for all subjects with CF. Because the group with a high viral infection rate was significantly younger (mean, 9.9 ± 3.3 years) than the low infection rate group (mean, 16.3 ± 5.0 years) (F[1,13] = 9.07; $P = .01$), the effect of age was covaried. The low infection rate group consisted of five male subjects and one female subject, while the high infection rate group contained five male subjects and four female subjects. The two groups of patients with CF, those with the lower viral infection rate and those with the higher rate had the same number of study visits (12.8 ± 2.8 vs 12.8 ± 2.5, respectively; F[1,13] = 0.0016; $P = .97$). Neither the percent of culture-proved viral infection (33.3% vs 26.5% for the low and high infection rate groups, respectively; $\chi^2 = 0.006$, $df = 1$; $P = .94$) nor the percent of symptomatic viral infections (41.7% vs 32.4% for the low and high infection rate groups, respectively; $\chi^2 = .05$, $df = 1$; $P = .82$) was significantly different between the two groups.

On enrollment, the group of subjects with CF with the higher rate of viral infections had better pulmonary function than those with less frequent infections. The $FEF_{25\%-75\%}$ was 39.3% ± 19.1% predicted in the group with more frequent infections, in comparison with 16.2% ± 8.8% predicted (F[1,13] = 7.6; $P = .02$). The FVC was also better in that group, 79.6% ± 21.6% predicted in comparison with those patients with less frequent infection (62.5% ± 25.4% predicted), but the difference was not statistically significant. The predominant bacterial pathogen colonizing the high infection rate group on enrollment was *S aureus* and the predominant pathogen colonizing the low infection rate group was *P aeruginosa* (Fisher's Exact Test, $P = .02$).

At the end of the 2-year observation period, the overall severity of CF had progressed less in the patients with more frequent infections. This was reflected in the average decrements per year in FVC, RV/TLC ratio, resting respiratory rate, and triceps fat fold thickness (Table 5). These four indexes demonstrated a significantly slower rate of decline in the patients with CF with more frequent infections (all $P < .05$).

Table 5.—Comparison of Rate of Change in Clinical Characteristics of Patients With Cystic Fibrosis Over 2 Years as a Function of the Frequency of Viral Infections

Clinical Variable	Rate of Viral Infections, Mean ± SD		ANOVA	
	≤1 per 5 Visits	≥1 per 5 Visits	F (*df*)	*P*
At enrollment				
FVC, % predicted	62.5 ± 25.4	79.6 ± 21.3	1.99 (1,13)	NS
$FEF_{25\%-75\%}$, % predicted	16.2 ± 8.8	39.3 ± 19.1	7.62 (1,13)	.02
RV/TLC, %	54.2 ± 16.6	48.3 ± 10.7	0.69 (1,13)	NS
Respirations/min	30.0 ± 6.6	29.3 ± 7.5	0.03 (1,13)	NS
Arm muscle circumference, cm	1.7 ± 1.6	8.3 ± 7.9	4.03 (1,13)	NS
Triceps fatfold thickness, mm	2.3 ± 2.1	10.9 ± 12.8	2.57 (1,13)	NS
Shwachman-Kulczycki score	64.2 ± 18.3	78.9 ± 12.2	3.55 (1,13)	NS
Mean (± SD) change per year*				
FVC, % predicted	−3.84 ± 3.72	−1.32 ± 9.00	4.63 (1,12)	.05
$FEF_{25\%-75\%}$, % predicted	−0.12 ± 3.72	0.24 ± 6.12	0.02 (1,12)	NS
RV/TLC, %	3.72 ± 3.12	0.24 ± 1.92	5.80 (1,12)	.03
Respirations/min	−0.84 ± 2.52	−3.36 ± 2.64	7.37 (1,12)	.02
Arm muscle circumference, cm	0.36 ± 2.28	9.00 ± 9.36	1.44 (1,11)	NS
Triceps fatfold thickness, mm	3.24 ± 5.04	11.16 ± 6.60	5.81 (1,12)	.03
Shwachman-Kulczycki score	−6.00 ± 4.92	−2.40 ± 4.32	1.17 (1,12)	NS
No. of Subjects	6	9	...	...

*Slopes (β coefficients) were derived by linear regression analysis. Mean slopes represent the rate of change in a parameter per year over 2 years for each group. A decreasing (or negative) value in forced vital capacity (FVC), forced expiratory flow, mid–expiratory phase ($FEF_{25\%-75\%}$), Shwachman-Kulczycki score, arm muscle circumference (AMC), and triceps fatfold thickness (TFT) reflect deterioration. An increasing value in residual volume/total lung capacity (RV/TLC) and respiratory rate reflect deterioration. In this age group, AMC and TFT should be increasing and respiratory rate decreasing due to growth during the 2-year period. NS indicates not significant.

COMMENT

The present study did not demonstrate an increased rate of respiratory viral or *M pneumoniae* infections in school-age patients with CF when compared with their unaffected siblings. The frequency of isolating viral pathogens from respiratory secretions and the rate of seroconversion were not significantly different between subjects with CF and their siblings. Two previous studies,[18,19] which suggested an increased frequency of viral infections in patients with CF, limited specimen collection to symptomatic periods. An increased rate of viral infection was not seen in the Toronto study,[22] where sampling occurred during both symptomatic and asymptomatic periods. The Toronto group was unsuccessful in isolating viruses from either patients with CF or their unaffected siblings and postulated an unidentified substance in secretions interfering with viral cultivation. The present study had a viral isolation rate of 7.8%, which is comparable with that found in other "viral watch" studies.[32,35] Our failure to culture respiratory syncytial virus and parainfluenza viruses may have been due to processing frozen specimens.[36] However, in previous studies[28,37,38] this laboratory has successfully cultured these viral pathogens after freezing.

The frequency of influenza A and B infections in the patients with CF was less than half that of the unaffected siblings. Since the majority of patients with CF had received the influenza vaccine and had elevated hemagglutination inhibition titers, this decrease in frequency of infection probably reflected the protective effect of the vaccine. Rhinoviruses were the only pathogens more commonly isolated in the group of patients with CF than in the sibling group, a finding also seen in adults with chronic obstructive pulmonary disease.[15]

The two characteristics of the subjects with CF that affected the frequency of respiratory viral infections were age and the predominant bacterial pathogen colonizing the lower respiratory tract. The youngest children, aged 6 to 10 years, had the highest infection rate. The association between age and respiratory viral infections is a consistent finding among epidemiologic studies of pediatric populations without CF.[6,7,28] The difference in viral infection rate between patients predominately colonized with *S aureus* and *P aeruginosa* was an unexpected finding. All study subjects attended school or work, negating a difference in exposure to respiratory viruses. Although *S aureus* colonized patients with CF were younger, this difference in acquisition rate persisted after covarying the effect of age. The viral infection rate for the *S aureus* colonized patients was the same as the unaffected siblings, whereas the patients with *P aeruginosa* had a significantly lower rate. The *P aeruginosa* colonized patients may have had a reduced immune response or an inhibitory factor interfering with viral isolation from respiratory secretions.

The present study did not find a positive association between the frequency of viral infections and a more rapid decline in pulmonary function. The annual rate of decline (slope of the regression line) for FVC in the high viral infection group was −1.31, which was similar to the rate reported in a large Canadian study[39] (−0.97 for men and −1.47 for women). In a manner similar to the Toronto study,[22] we divided the subjects with CF into two groups based on frequency of viral infection and compared the 2-year trend in pulmonary function tests and other inhibitors of disease severity. Unexpectedly, the clinical characteristics of the two groups in our study were significantly different in that the group with a higher frequency of viral infection was younger, healthier, and more frequently colonized with

S aureus, whereas the group with the lower rate of infection was colonized with *P aeruginosa*. The annual rate of decline of −3.84 for the low infection rate group was greater than predicted from the previously published data[39] and may reflect the adverse effect of *P aeruginosa* on these patients. This difference in bacterial colonization may also explain the discrepancy between our results and the findings reported by the Toronto group.[22] In that study, the patients with a higher frequency of infection had an annual decline in percent FVC of −20.5 (10 times greater than the decline in the present study). The Canadian patients with CF also demonstrated a positive correlation between frequency of viral infection and colonization with *Pseudomonas cepacia*, a bacterial pathogen known to have a detrimental effect on the patient's pulmonary status.[40] None of the Seattle patients were colonized with *P cepacia*.

A second distinction between the two study populations may be their influenza vaccination status. The majority of the Seattle patients were immunized. The vaccine status of the Toronto patients was not reported. It is conceivable that a larger number of nonimmunized subjects with CF in the Canadian study may have suffered greater pulmonary morbidity from influenza virus infection.

In conclusion, patients with CF in the present study did not have an increased rate of infection with common respiratory viruses. This study was limited to children over 5 years of age, and our findings should not be extrapolated to infants with CF. Respiratory viral infections, primarily repiratory syncytial virus, are more prevalent in the first 2 years of life[6,7,28] and lead to significant morbidity even in healthy infants. Further studies must be directed toward viral infections in infants with CF to determine the role of viruses in initial bacterial colonization and progressive lung disease.

This research project was supported by a grant from the Cystic Fibrosis Foundation, Bethesda, Md.

References

1. Wood RE, Boat TF, Doershuk CF. Cystic fibrosis: state of the art. *Am Rev Respir Dis.* 1976;11:833-877.
2. Marks MI. The pathogenesis and treatment of pulmonary infections in patients with cystic fibrosis. *J Pediatr.* 1981;98:173-179.
3. Moss RB, Lewiston NJ. Immune complexes and humoral response to *Pseudomonas aeruginosa* in cystic fibrosis. *Am Rev Respir Dis.* 1980;121:23-29.
4. Schiotz PO, Neilson H, Hoiby N, et al. Immune complexes in sputum of patients with cystic fibrosis suffering from chronic *Pseudomonas aeruginosa* lung infection. *Acta Pathol Microbiol Immunol Scand.* 1978;86:37-40.
5. Pennington JE, Wolff SM, Puziss M. Summary of a workshop on infections in patients with cystic fibrosis. *J Infect Dis.* 1979;140:252-256.
6. Glezen WP, Denny FW. Epidemiology of acute lower respiratory disease in children. *N Engl J Med.* 1973;288:498-505.
7. Murphy TF, Henderson FW, Clyde WA, Collier WA, Collier AM, Denny FW. Pneumonia: an eleven year study in pediatric practice. *Am J Epidemiol.* 1981;113:12-21.
8. Westerberg SC, Smith CB, Renzetti AD. *Mycoplasma* infections in patients with chronic obstructive pulmonary disease. *J Infect Dis.* 1973;127:491-497.
9. Stenhouse AC. Rhinovirus infection in acute exacerbations of chronic bronchitis: a controlled prospective study. *Br Med J.* 1967;3:461-463.
10. Smith CB, Golden CA, Kanner RE, Renzetti AD. Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. *Am Rev Respir Dis.* 1988;121:255-232.
11. Buscho RO, Saxtan D, Shultz PS, Finch E, Mufson MA. Infections with viruses and *Mycoplasma pneumoniae* during exacerbations of chronic bronchitis. *J Infect Dis.* 1978;137:377-383.
12. Carilli AD, Gohd RS, Gordon W. A virologic study of chronic bronchitis. *N Engl J Med.* 1964;270:123-127.
13. McNamara MJ, Phillips IA, Williams OB. Viral and *Mycoplasma pneumoniae* infections in exacerbations of chronic lung disease. *Am Rev Respir Dis.* 1969;100:19-24.
14. Gump DW, Phillips CA, Forsyth BR, McIntosh K, Lamborn KR, Stouch WH. Role of infection in chronic bronchitis. *Am Rev Respir Dis.* 1976;115:465-474.
15. Monto AS. Susceptibility to rhinovirus infection in chronic bronchitis. *Am Rev Respir Dis.* 1978;118:1101-1103.
16. Eadie MB, Stott EJ, Grist NR. Virological studies in chronic bronchitis. *Br Med J.* 1966;2:671-673.
17. Minor TE, Baker JW, Dick EC, et al. Greater frequency of viral respiratory infections in asthmatic children compared with non-asthmatic siblings. *J Pediatr.* 1974;85:472-477.
18. Deforest A, Grosz HC, Laraya-Cuasay LR, Huang NN. A serologic study of *Mycoplasma pneumoniae* and respiratory syncytial virus infection in patients with cystic fibrosis. In: *Cystic Fibrosis Club Abstracts.* Atlanta, Ga: Cystic Fibrosis Foundation; 1976:31.
19. Efthimiuo J, Hodson ME, Taylor P, Taylor AG, Battan JE. Importance of viruses and *Legionella pneumophila* in respiratory exacerbations of young adults with cystic fibrosis. *Thorax.* 1984; 39:150-154.
20. Peterson NT, Hoiby N, Mordhorst CH, Lind K, Flensborg EH, Bruun B. Respiratory infections in cystic fibrosis patients caused by virus, *Chlamydia*, and *Mycoplasma*: possible synergism with *Pseudomonas aeruginosa*. *Acta Paediatr Scand.* 1981;70:623-628.
21. Wright PF, Khaw KT, Oxman MN, Schwachman H. Evaluation of the safety of amantadine HCl and the role of respiratory viral infections in children with cystic fibrosis. *J Infect Dis.* 1976;134:144-149.
22. Wang EL, Prober CG, Manson B, Corey M, Levison H. Association of respiratory viral infections with pulmonary deterioration in patients with cystic fibrosis. *N Engl J Med.* 1984;311:1653-1658.
23. Schwachman H, Kulczycki LL. Long-term study of one hundred five patients with cystic fibrosis. *AJDC.* 1958;96:6-15.
24. Renzetti AD Jr. Snowbird Workshop on Standardization of Spirometry: American Thoracic Society. *Am Rev Respir Dis.* 1979;119:831-838.
25. Weng TR, Levison H. Standards of pulmonary function in children. *Am Rev Respir Dis.* 1969;99:879.
26. Polgar G, Promhadt V. *Pulmonary Function Testing in Children: Techniques and Standards.* Philadelphia, Pa: WB Saunders Co; 1971:87-212.
27. Schmidt, N. Cell culture techniques. In: Lennette EH, Schmidt NJ, eds. *Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infection.* 5th ed. Washington, DC: American Society of Microbiology; 1979:65-140.
28. Foy HM, Cooney MK, Maletsky AJ, et al. Incidence and etiology of pneumonia, croup, and bronchiolitis in preschool children belonging to a prepaid medical care group over a 4 year period. *Am J Epidemiol.* 1973;97:80-102.
29. Wong K, Roberts MC, Owens L, Fife M, Smith AL. Selective media for the quantitation of bacteria in cystic fibrosis sputum. *J Med Microbiol.* 1984;17:113-119.
30. Lennett EH, Balows A, Hausler WJ, Tuant SP. *Manual of Clinical Microbiology.* 3rd ed. Washington, DC: American Society of Microbiology; 1980:83-87,288-317,330-336.
31. Pedhazur, EJ. *Multiple Regression in Behavioral Research.* 2nd ed. New York, NY: Holt Rinehart & Winston; 1982.
32. Foy HM, Fox JP, Cooney MK. Efficacy of X-2 interferon against the common cold. *N Engl J Med.* 1986;315:513-514.
33. Foy HM, Cooney MK, Taylor J, et al. Antibody response to Influenza A/New Jersey and A/Victoria virus vaccines in 1976 and subsequent antibody levels after Influenza A epidemics, 1977-1979. *J Infect Dis.* 1980;142:139-144.
34. Foy HM, Cooney MK, Allan I. Longitudinal studies of types A and B influenza among Seattle school children and families: 1968-1974. *J Infect Dis.* 1976;134:362-369.
35. Cooney MK, Hall CE, Fox JP. Seattle viral watch, III: isolation methods and infections detected. *Am J Epidemiol.* 1972;93:286-305.
36. Parrott R, Kim H, Brandt C, et al. Respiratory syncytial virus. In: Lennette EH, Schmidt NJ, eds. *Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infection.* 5th ed. Washington, DC: American Society of Microbiology; 1979:695-708.
37. Ramsey BW, Marcuse EK, Foy H, et al. Use of bacterial antigen detection in the diagnosis of pediatric lower respiratory infections. *Pediatrics.* 1986;78:1-9.
38. Kimball AM, Foy HM, Cooney MK, Allan D, Matlock M, Plorde JJ. Isolation of respiratory syncytial and Influenza viruses from the sputum of patients hospitalized with pneumonia. *J Infect Dis.* 1983;147:181-184.
39. Corey M, Levison H, Crozier D. Five to seven year course of pulmonary function in cystic fibrosis. *Am Rev Respir Dis.* 1976;114:1085-1092.
40. Isles A, Maclusky I, Corey M, et al. *Pseudomonas cepacia* infection in cystic fibrosis: an emerging problem. *J Pediatr.* 1984;104:206-210.

Marked Transient Alkaline Phosphatemia Following Pediatric Liver Transplantation

Baburao Koneru, MD; Eduardo Carone, MD; J. Jeffrey Malatack, MD; Carlos O. Esquivel, MD, PhD; Thomas E. Starzl, MD, PhD

• An isolated marked transient rise in serum alkaline phosphatase levels in otherwise healthy children is a well-documented occurrence. However, in children undergoing liver transplantation, elevated alkaline phosphatase values raise the possibility of biliary obstruction, rejection, or both. During a 6-year period, 6 of 278 children undergoing liver transplantation exhibited a similar phenomenon as an isolated abnormality. None had rejection, biliary obstruction, or other allograft dysfunction during a long follow-up. Eventually and without intervention, the alkaline phosphatase levels returned to normal. These instructive cases suggest that caution be used in advocating invasive procedures if elevated alkaline phosphatase levels are an isolated abnormality, and close observation with noninvasive testing is recommended.

(*AJDC*. 1989;143:669-670)

After orthotopic liver transplantation, liver function test results are serially determined to monitor allograft function. Serum alkaline phosphatase (AP) and γ-glutamyltransferase (GGT) levels, when markedly elevated, lead to a strong suspicion of either allograft rejection or biliary obstruction. Further investigations, sometimes invasive, are often required to elucidate the exact problem.

An isolated, transient, marked elevation of serum AP levels without any evidence of biliary obstruction has been reported in infants and children who have not undergone transplantation.[1-7] Infusions of serum albumin[8] and therapy with sulfamethoxazole-trimethoprim[9] have been reported to cause elevation of AP levels, but the cause in most patients is unknown. We have encountered six children who had an isolated, transient, marked elevation of serum AP levels at varying intervals following liver transplantation without evidence of biliary obstruction or rejection. The intent of this article is to bring this problem to the attention of physicians caring for pediatric liver transplant recipients and to urge caution in advocating invasive procedures.

PATIENTS AND METHODS

During the years 1981 through 1986, 278 children received 378 liver transplants in the University of Pittsburgh (Pa) Children's Hospital transplant program.

Part of the postoperative follow-up after discharge consisted of periodic checks of body weight, a complete blood cell count, and determinations of prothrombin and partial thromboplastin times, serum total bilirubin, alanine and aspartate aminotransferases, AP, GGT, calcium, and phosphorus. In that 6-year period, six children exhibited a marked transient rise (>1500 U/L) in serum AP levels in the posttransplant period, with other liver function study results, including the GGT determination, being normal. Whenever an isolated elevation of serum AP levels was encountered, an abdominal ultrasound was performed for evidence of intrahepatic biliary ductal dilatation. Skeletal roentgenograms were obtained for all six children, and a serum AP isoenzyme fractionation was performed in four of six children with elevations in serum AP levels.

The age range of children presenting with transient elevations of serum AP levels was 2 to 6 years, with an average age of 38 months. The clinical details of these children are given in the Table. Five had biliary atresia and one had α_1-antitrypsin deficiency. As a rule, the transient elevation in serum AP levels occurred following discharge from the hospital. The time interval between transplantation and the rise in AP levels varied between 3½ to 14 months. There were no major alterations in the list of drugs these patients were receiving before the rise in AP levels. With ultrasound, none of the children had evidence of biliary ductal dilatation suggestive of obstruction. The bilirubin, alanine aminotransferase, aspartate aminotransferase, and GGT values remained normal. A liver biopsy or cholangiogram during or after the period of rise in serum AP values was not performed. Of the four children in whom iso-

Clinical Details of Six Patients With Transient Elevation of Serum AP Levels*

Patient No./Age, y/Sex	Time Interval From Transplant, mo	Highest AP Level, U/L	Predominant Isoenzyme Fraction	Duration of AP Elevation	Follow-up After Normalization of AP, mo
1/6/M	12	2500	Not done	4 wk	54
2/3/M	12	4095	Not done	4 wk	50
3/2¼/M	12	1737	Bone	2 wk	30
4/2¼/F	14	4651	Liver	10 wk	26
5/3⅓/F	3½	8680	Bone	8 wk	28
6/2/F	5	4550	Bone	16 mo	9

*AP indicates alkaline phosphatase.

Accepted for publication December 24, 1988.

From the Departments of Surgery (Drs Koneru and Starzl) and Pediatrics (Dr Malatack), University of Pittsburgh, Pa; the Department of Surgery, University of São Pãulo, Brazil (Dr Carone); and the Division of Transplantation, Pacific Presbyterian Medical Center, San Francisco, Calif (Dr Esquivel). Dr Koneru is now with the Liver Transplant Division, Univesity Hospital, Univeristy of Medicine & Dentistry of New Jersey, Newark.

Reprints not available.

enzyme fractionation data were available, three showed an increased bone fraction. The fourth child showed an increase in the liver fraction of serum AP. Of the six children, five had long-bone roentgenograms that did not support a diagnosis of rickets (the sixth patient had a skeletal survey at the time of transplant that gave normal results). The duration in which the AP levels remained elevated ranged from 2 weeks to 16 months. In the follow-up period after normalization of the serum AP values (9 to 54 months), none of the children exhibited any features of obstruction or rejection. All the children improved without having to undergo any surgical procedures. All six children are alive and doing well, with normal allograft function.

COMMENT

In 1954, Bach[1] first reported the occurrence of an isolated marked transient elevation of serum AP levels in three infants. About 1.5% of 500 serum samples from healthy children had marked elevation of serum AP levels in a study conducted by Asanti et al[2] in 1966. In our follow-up of children who had received liver transplants, the incidence of isolated marked transient elevations of AP levels was 2.1%. Isoenzyme fractionation studies of cases reported in the literature have revealed the source of this elevated enzyme level to be bone, liver, or both.[3,7] In four of our patients in whom isoenzyme fractionation data were obtained, bone fraction was predominant in three patients and liver fraction in one patient. It is not known why a marked rise suddenly occurred in the serum level of this enzyme, as previously reported in the healthy children and now in the transplant recipients.

Confronted with the elevation of serum AP levels after liver transplantation, the clinician is prompted to consider the pathologic conditions of the liver, skeleton, or both. Paramount among these considerations are biliary obstruction and allograft rejection. Biliary obstruction can often be detected by the noninvasive means of ultrasound. Utilization of more invasive methods, including percutaneous transhepatic cholangiography or surgery, should only be considered if the ultrasonogram reveals obstruction, or continued clinical or laboratory follow-up reveals additional evidence supportive of biliary obstruction. Rejection often presents as an elevation of the canalicular enzyme levels, including the serum AP levels, before a significant rise in transaminase levels. A rise in GGT levels in allograft rejection mimics the elevation in serum AP levels. The isolated nature of the elevation of serum AP levels in our patients was reassuring and allowed us to avoid performing an allograft biopsy in favor of close clinical or laboratory follow-up. Subsequently, long-term follow-up of these children has supported this conservative approach, since none have shown evidence of either obstruction or rejection.

Other considerations as causative for the isolated elevation of serum AP levels include bone reactivity, infusion of serum albumin,[8] and sulfamethoxazole-trimethoprim therapy.[9] While rapid correction of rickets after liver transplantation is a well-known occurrence, none of our patients had rickets, as determined by use of roentgenography. The possibility of subclinical rickets, however, still exists. Also, none of the children demonstrated a rapid growth spurt beginning at the time of the rise in serum AP levels. None of our patients were receiving albumin infusions at the time of the rise in serum AP levels, and only one patient was receiving sulfamethoxazole-trimethoprim.

In line with reports in the literature,[1-7] in all of our patients, elevated serum AP values ultimately returned to normal without medical or surgical intervention. When physicians caring for children who have received liver transplants are confronted with elevated serum AP levels but normal liver transaminase, GGT, and bilirubin levels and a normal ultrasonogram, they should choose close observation and frequent laboratory follow-up as the most prudent medical course.

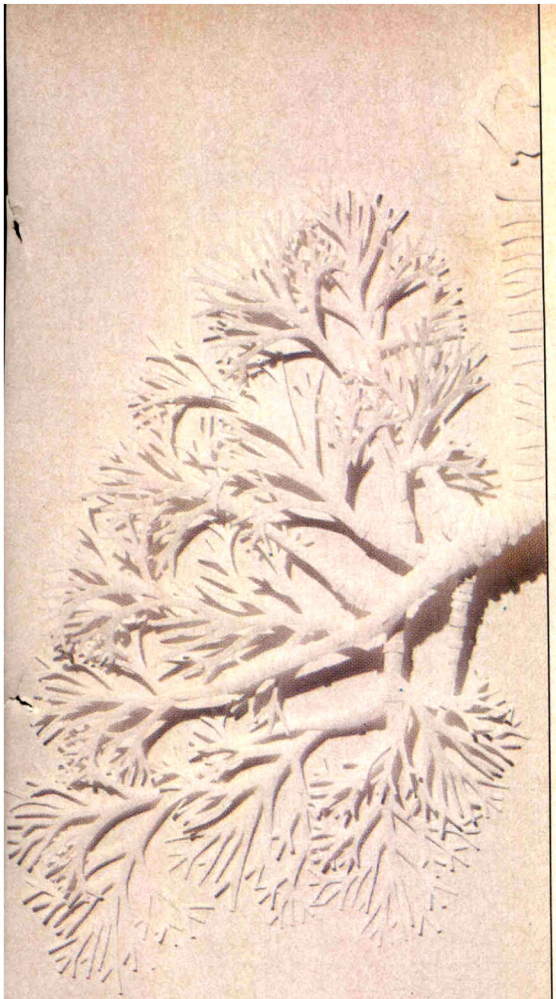
This study was supported by research grants from the Veterans Administration and project grant AM-29961 from the National Institutes of Health, Bethesda, Md.

References

1. Bach U. Das Verhalten der alkalischen serumphosphatase bei Fruhgeborenen Rachitikern und Spasmophilen. *Eur J Pediatr.* 1954;74:593-609.
2. Asanti R, Hultim H, Visakorpi JK. Serum alkaline phosphatase in healthy infants: occurrence of abnormally high values without known cause. *Ann Pediatr Fenn.* 1966;12:139-142.
3. Posen S, Lee C, Vines R, et al. Transient hyperphosphatasemia of infancy: an insufficiently recognized syndrome. *Clin Chem.* 1977;23:292-294.
4. Rosalki SB, Foo Y. Transient hyperphosphatasemia of infancy: four new cases and a suggested etiology. *Clin Chem.* 1980;26:1109-1110.
5. Abbasi V, Colon AR, Schwartz RH. Benign elevation of serum alkaline phosphatase: transient and persistent variety. *Clin Pediatr.* 1984;23:336-337.
6. Steinherz PG, Steinherz LJ, Nisselbaum JS, et al. Transient, marked, unexplained elevation of serum alkaline phosphatase. *JAMA.* 1984;252:3289-3292.
7. Kraut JR, Metrick M, Maxwell NR, et al. Isoenzyme studies in transient hyperphosphatasemia of infancy: ten new cases and a review of the literature. *AJDC.* 1985;139:736-740.
8. Neale FC, Clubb JS, Posen S. Artificial elevation of the serum alkaline phosphatase concentration. *Med J Aust.* 1968;2:684.
9. DeVito GA: Transient elevation of alkaline phosphatase possibly related to trimethoprim-sulfamethoxazole therapy. *J Pediatr.* 1982;100:998-999.

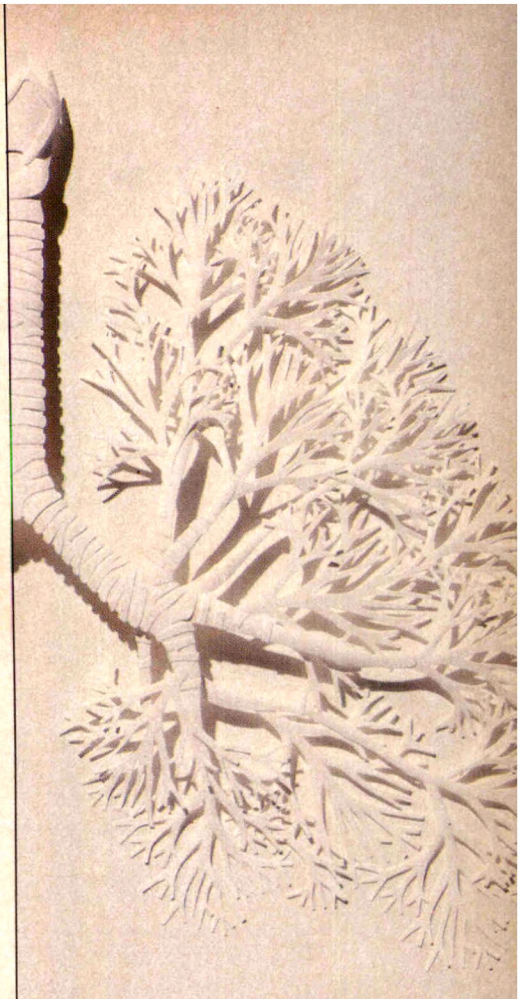
In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY
Heterotopic Lingual Brain in the Newborn
Robert Knox, MD; Michael Pratt, MD; A. Julian Garvin, MD, PhD; Benjamin White, MD
(*Arch Otolaryngol Head Neck Surg.* 1989;115:630-632)



TWO SIDES OF ASTHMA THERAPY

FOUNDATION THERAPY
SYMPTOMATIC THERAPY



Asthma is more than just a series of symptomatic episodes. In fact, asthma is a four-part cycle... starting with the early response of bronchospasm, followed by bronchial inflammation, a late response, and bronchial hyperreactivity (which increases the likelihood of another episode). *Only INTAL® acts on all four of these processes.*

Prescribed as foundation therapy, INTAL improves pulmonary function and reduces asthma severity over time,[1] while providing safety in both children and adults.

FOUNDATION

INTAL®

(cromolyn sodium /FISONS)

COMPLEMENTS SYMPTOMATIC THERAPY

Symptomatic therapy—bronchodilators—acts only against the early response of bronchospasm. By combining symptomatic and foundation therapy, the four-part cycle of asthma is broken, and patients receive both immediate relief and long-term improvement.

INTAL is available in three convenient dosage forms, to meet the variety of patients' needs.

Prescribe INTAL in addition to symptomatic therapy...and see how effectively one complements the other.

FISONS
Pharmaceuticals
Rochester, NY 14623

See adjacent page for brief summary of Full Prescribing Informatio

INTAL® Inhaler
(cromolyn sodium/FISONS)
800 mcg/Puff

DESCRIPTION: INTAL Inhaler (cromolyn sodium inhalation aerosol) is a metered dose aerosol unit for oral inhalation containing micronized cromolyn sodium, sorbitan trioleate with dichlorotetrafluoroethane and dichlorodifluoromethane as propellants. Each metered spray delivers to the patient approximately 800 mcg of cromolyn sodium. Each 8.1g canister delivers at least 112 metered sprays (56 doses); each 14.2g canister delivers at least 200 metered sprays (100 doses).

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium.

No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were: throat irritation or dryness, bad taste, cough, wheeze, nausea.

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV_1)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

DOSAGE AND ADMINISTRATION: For management of bronchial asthma in adults and children (5 years of age and over) who are able to use the Inhaler, the usual starting dosage is two metered sprays inhaled four times daily at regular intervals.

Patients with chronic asthma should be advised that the effect of INTAL Inhaler therapy is dependent upon its administration at regular intervals, as directed. INTAL Inhaler should be introduced into the patient's therapeutic regimen when the acute episode has been controlled, the airway has been cleared and the patient is able to inhale adequately.

For the prevention of acute bronchospasm which follows exercise, exposure to cold dry air or environmental agents, the usual dose is the inhalation of two metered dose sprays shortly, i.e., 10-15 minutes but not more than 60 minutes, before exposure to the precipitating factor.

INTAL INHALER THERAPY IN RELATION TO OTHER TREATMENTS FOR ASTHMA: Non-steroidal agents: INTAL Inhaler should be **added** to the patient's existing treatment regimen (e.g., bronchodilators). When a clinical response to INTAL Inhaler is evident, usually within two to four weeks, and if the asthma is under good control, an attempt may be made to decrease concomitant medication usage gradually.

Corticosteroids: In patients chronically receiving corticosteroids for the management of bronchial asthma, the dosage should be maintained following the introduction of INTAL Inhaler. If the patient improves, an attempt to decrease corticosteroids should be made.

It is particularly important that great care be exercised if for any reason cromolyn sodium is withdrawn in cases where its use has permitted a reduction in the maintenance dose of corticosteroids.

HOW SUPPLIED: INTAL Inhaler, 8.1g or 14.2g canister, box of one. Supplied with inhalation adapter and patient instructions.

NDC 0585-0675-01 14.2g canister NDC 0585-0675-02 8.1g canister

Store between 2°-30°C (36°-86°F). Contents under pressure. Do not puncture or incinerate. Keep out of the reach of children.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for: FISONS CORPORATION ROCHESTER, NY 14623 U.S.A.

By: Riker Laboratories One Morley Street Loughborough, England LE11 1EP

© Fisons Corporation 1986 — All Rights Reserved
INTAL® is a registered trademark of Fisons plc.

Made in England Rev 7/86 FC 7518B

Reference: 1. Eigen H, Reid JJ, Dahl R, et al: Evaluation of the addition of cromolyn sodium to bronchodilator maintenance therapy in the long-term management of asthma. *J Allergy Clin Immunol* 1987;80:612-621.

© 1989 Fisons Corporation FIS-047

FISONS
Pharmaceuticals
Prescription Products
Rochester, NY 14623

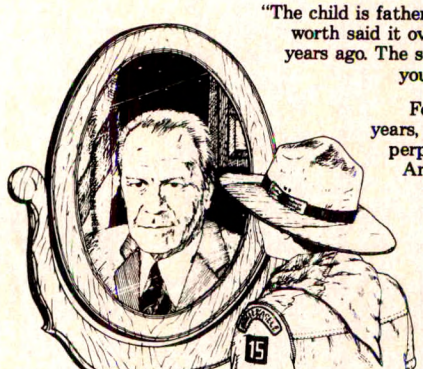
PEDIATRICIAN

Immediate opportunity to associate with five pediatricians in an accredited 70-doctor multispecialty group. Drawing area of 400,000. Modern hospital within five minutes of Clinic. Stimulating Big-10 university community of 110,000 with superb cultural advantages. Ideal for families. Medical school teaching affiliation if desired. Excellent initial guarantee and fringes with early associate status, subsequent income based exclusively on productivity. Subspecialty training in allergy desirable. Send CV to:

Ronald H. Deering, Sr., M.D.
Christie Clinic Association
101 W. University
Champaign, IL 61820

REFLECTIONS OF GREATNESS

Gerald Ford, President: 1974 - 1977.
Eagle Scout, 1927.



"The child is father of the man." Wordsworth said it over one- hundred fifty years ago. The strengths ingrained in youth flourish with age.

For more than seventy years, the Boy Scouts have perpetuated the ideals of America: honor, character, loyalty; duty to God, mankind, and country.

It's not surprising some of our nation's outstanding citizens and leaders have been Boy Scouts.

BECOME A MEMBER OF THE NATIONAL BOY SCOUT ALUMNI FAMILY. — JOIN TODAY!

Your one-year, $10 membership entitles you to the Alumni Bulletin, the Annual Report, a membership card and an attractive wall certificate suitable for framing.

A three-year, $30 membership entitles you to a free Norman Rockwell print, as well as all of the benefits of a one-year membership.

Write today to:
National Boy Scout Alumni Family
1325 Walnut Hill Lane • Irving, Texas 75062 - 1296

Sports Medicine

William B. Strong, MD, Augusta, Ga
Carl L. Stanitski, MD, Pittsburgh, Pa
Ronald E. Smith, PhD, Seattle, Wash
Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—*The need to estimate maximum oxygen consumption ($\dot{V}O_2max$) concerns many individuals who work with youth fitness. This study presents a methodology that will help in unifying data. It also demonstrates the relationship of $\dot{V}O_2max$ to lean body mass and the discrepancy that occurs when attempting to index by body weight.*—W.B.S.

Predicting Maximum Oxygen Uptake in Adolescents

Albert C. Hergenroeder, MD, Robert B. Schoene, MD

• The purpose of this study was to develop regression equations to predict oxygen uptake ($\dot{V}O_2$) in adolescents. Thirty-nine subjects had maximum oxygen uptake measured on a cycle ergometer. Anthropometric measurements included triceps, subscapular, and thigh skin folds. The subjects ran 12-minute and 2.4-km runs on separate days. Using a multiple-stepwise forward regression analysis, equations were developed to predict oxygen uptake as $\dot{V}O_2$ and $\dot{V}O_2$/kg, accounting for 81% and 64% of the variance, respectively. A validation procedure was done 5 months later when all runs and measurements were repeated, and predicted and measured oxygen uptake were compared. The equation for predicting $\dot{V}O_2$ accounted for 88% of the variance, with the SE of the estimate equal to 0.07 L/min. The equation for predicting $\dot{V}O_2$/kg accounted for 58% of the variance, with the SE of the estimate equal to 27 mL of oxygen per kilogram of body weight per minute. The $\dot{V}O_2$ can be accurately predicted using indirect means in adolescents, while $\dot{V}O_2$/kg cannot.

(*AJDC*. 1989;143:673-677)

Maximal aerobic power is the best index of cardiovascular fitness.[1,2] Maximal oxygen uptake ($\dot{V}O_2$) is the most commonly used measure of maximal aerobic power.[3(p3)] Maximal oxygen uptake is expressed in two forms: (1) as $\dot{V}O_2$ (liters per minute), which is the level of oxygen uptake that cannot be surpassed even when the exercise load is increased, and (2) as $\dot{V}O_2$/kg (milliliters of oxygen per kilogram of body weight per minute), which is the maximal oxygen uptake normalized for body weight. The direct measurements of oxygen uptake, using an ergometer and expired gas measurements, is accurate and reproducible but expensive and logistically difficult, especially for large numbers of subjects. Investigators have tested indirect and less expensive methods of estimating oxygen uptake so that an estimate of cardiovascular fitness could be made for large groups of subjects. One approach is to utilize submaximal tests, which are inaccurate in estimating maximal aerobic power.[3(p334)] Indirect methods of estimating aerobic power are available; however, studies in adolescents have not predicted $\dot{V}O_2$/kg accurately, have not given a measure of accuracy, or have used selected populations. Studies on adolescents have generated correlations between $\dot{V}O_2$/kg and a run performance, but none have developed an equation to predict $\dot{V}O_2$/kg.[4-8] One study did develop an equation to predict $\dot{V}O_2$/kg from run performance, but the multiple r value of .62 was unacceptably low for predictive purposes.[9] Four of these six studies included male subjects only, and the female subjects studied in the other two studies were 10 to 12 years old. The purpose of this study was to develop improved methods of predicting oxygen uptake.

SUBJECTS AND METHODS

Without any prior knowledge of the subjects, we chose 39 students, 12 to 16 years of age, from three separate junior/senior high

Accepted for publication March 6, 1989.

From the Division of Adolescent Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, Tex (Dr Hergenroeder), and the Division of Respiratory Diseases, Department of Medicine, Harborview Medical Center, University of Washington, Seattle (Dr Schoene).

Presented before the Section of Adolescent Medicine, Society of Pediatric Research, Anaheim, Calif, April 30, 1987.

Reprint requests to Division of Adolescent Medicine, Department of Pediatrics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030 (Dr Hergenroeder).

Table 1.—Physical Characteristics*

Variable	Males	Females
Height, cm (range)	170 ± 12 (143-187)	163 ± 8 (150-171)
Weight, kg (range)	60.7 ± 15.2 (40-95.7)	58.2 ± 53.5 (38.6-104.1)
% body fat estimate	21 ± 6	28 ± 4

*Values are expressed as mean ± SD.

Table 2.—Oxygen Uptake Measurements at the Beginning of the Study*

Group	$\dot{V}O_2$, L/min	$\dot{V}O_2$/kg, mL/kg of BW per min
Males	3.0 ± 0.8	52.6 ± 8.1
Females	2.3 ± 0.3	41.2 ± 6.0

*Values are expressed as mean ± SD. $\dot{V}O_2$ indicates oxygen consumption; BW, body weight.

Table 3.—Simple Correlations Between Measured Oxygen Consumption ($\dot{V}O_2$), $\dot{V}O_2$/kg, and Independent Variables

	r	
	$\dot{V}O_2$/kg	$\dot{V}O_2$
2.4-km run speed	.75*	.44†
Weight	.04	.72*
Height	.48†	.83*
Sexual maturity rating	.20	.56†
Age	.08	.49†
Gender (1 M, 2 F)	−.63*	−.48†
Thigh circumference	−.23	.46†
Anterior midthigh skin fold	−.71*	−.36‡
Lean body mass	.27	.84*

*$P<.001$.
†$P<.007$.
‡$P<.02$.

schools by random selection from physical education classes in the seventh to 10th grades. All students in these grades participated in physical education classes. All subjects were interviewed by one of us (A.C.H.) or one trained research assistant. The initial interview identified conditions in the medical and family history that would preclude participation in a fitness study or a maximal exercise test. These conditions included a fracture and other recent musculoskeletal trauma, intractable headaches requiring admission to a hospital, spastic diplegia, weight loss and weakness of unknown origin, and significant exercise-induced asthma. Regarding the last condition, two students excluded themselves. Socioeconomic status was estimated using the *Two Factor Index of Social Position* of Hollingshead.[10] Students and their parents gave informed consent as approved by the Human Subjects Review Committees of the University of Washington, Seattle, and the Washington State Office of Maternal and Child Health, Olympia.

Initial measurements included blood pressure, resting pulse, weight, height, midthigh circumference, triceps, subscapular, and midthigh skin folds. Sexual maturity was estimated using the method of Duke et al.[11] All skin-fold measurements were done by one nutritionist using Lange calipers. She calibrated her measurements against those of another nutritionist, and they were within 1 mm of each other on all measurements. Body density was estimated using the method of Parizkova[12] and percent body fat was estimated using the method of Siri.[13]

All students ran the 2.4-km and 12-minute runs as an estimate of their cardiovascular fitness. The runs were supervised by a physical education instructor and a member of the research staff and were done on separate days. The students were told their grade depended on their effort. The students performed the runs as a group on a track near the school. For the 2.4-km run, the students were timed running six laps around the track. For the 12-minute run, the students ran as far as they could in 12 minutes, and at the 12-minute mark their total distance was estimated to the nearest 55 yards. After completing the interview and runs, on separate days the students had maximal oxygen uptake measured on a cycle ergometer at an exercise physiology laboratory. The exercise protocol was explained to the subjects, after which they were placed on an electronically braked cycle ergometer (Quinton Corp, Seattle). The ergometer had been calibrated for specific work loads. The subject's electrocardiogram was monitored continuously. Exercise variables were measured with an exercise system (System 2000, Medical Graphics Corporation, St Paul, Minn), with capabilities to measure breath-by-breath data during a progressive work test. The subjects breathed through the mouthpiece connected to a three-way valve (Hans Rudolph, Kansas City, Mo) with a dead space of 50 mL. Expired gases were measured for volume and expired gas fractions on a breath-by-breath basis. Within this system, flow was measured with a pneumotachograph (Model 4800, Hans Rudolph), which had been calibrated with a 3-L syringe. Expired oxygen and carbon dioxide concentrations were monitored at the mouth by a gas sampling line that led to an infrared carbon dioxide analyzer (Datex CD 101, Helsinki, Finland) and electrochemical cell fuel oxygen analyzer (Model 5-3A, Applied Electrochemistry Inc, Sunnyvale, Calif). Both analyzers were calibrated before each study with the gas of known oxygen and carbon dioxide concentrations. A wave form analyzer (Model CD101, Validyne, Northridge, Calif) received analog information from the flow signals, gas analyzers, and the heart rate monitor. These data were transferred to a host computer system (Tektronix 4052, Beverton, Ore) for display, tape storage, and computation. The data analysis was performed on software designed by Medical Graphics Company (St Paul, Minn), with computer programs to measure metabolic variables. After an initial 1-minute rest period, the subjects began pedaling at 50 to 70 rpm at 100 kilopond-meters per minute work load, which was increased 100 kilopond-meters per minute each minute until exhaustion. The $\dot{V}O_2$max was determined by two experienced technicians. Since the Medical Graphics System 2000 has immediate digital and graphical printouts of measured variables on a breath-by-breath basis, the subjects were considered to be at maximum when $\dot{V}O_2$ stopped rising as the work rate was increased. All subjects achieved a minimum respiratory exchange ratio of 1.0 and 85% reached a minimum respiratory exchange ratio of 1.1 or greater.

The reliability of the $\dot{V}O_2$ measurements was within 2%. The system was cross-checked by the manufacturer and the exercise laboratory staff with balloon collections and a Tissot gasometer (Warren E. Collins Inc, Braintree, Mass).

Simple correlations were analyzed between oxygen uptake and selected anthropometric measurement and run performance variables. Using variables significantly related to oxygen uptake, a multiple-stepwise forward regression analysis was performed and equations were developed to predict oxygen uptake, expressed as $\dot{V}O_2$ and $\dot{V}O_2$/kg. All measurements, runs, and oxygen uptake measurements were repeated 5 months later on the same 39 students, and the actual and predicted oxygen uptake values compared. Finally, we predicted oxygen uptake using other authors' regression equations and compared them with the oxygen uptake values at 5 months.

Statistical Analysis

The data were analyzed using a statistical analysis system (SAS Institute, Cary, NC) software package, including multiple-stepwise forward regression analyses for the derivation of the regression equations. All values are given as mean ± SD.

RESULTS

The mean ± SD age of the subjects was 14.5 ± 1.2 years. Eighty-five percent of the subjects were white, and 85% were in the highest two socioeconomic levels on Hollingshead's *Two Factor Index of Social Posi-*

tion. Twenty-seven subjects were male. The average height, weight, and estimated percent body fat are listed in Table 1. Twenty-nine students estimated their Tanner stage to be IV or V, 5 estimated Tanner stage III, 2 each estimated Tanner stages II and I, and 1 refused to estimate. The oxygen uptake measurements were comparable with those of other studies (Table 2).[14] The 2.4-km run speed had the highest correlation with $\dot{V}O_2$/kg, while lean body mass (LBM) had the highest correlation with $\dot{V}O_2$ (Table 3).

Using a multiple-stepwise forward regression analysis and including all the variables in Table 3, the following equations were developed:

$$\dot{V}O_2/kg = 49.8 + 0.11\,(2.4\ speed) - 7.2\,(gender) - 0.3(TCA)$$
$$R^2 = 0.64$$
$$\dot{V}O_2 = -0.07 + 0.004\,(2.4\ speed) - 0.42\,(gender) + 0.06\,(LBM)$$
$$R^2 = 0.81$$

The 2.4 speed was the speed on the 2.4-km run in meters per minute; for gender, there were 1 male and 2 female subjects; TCA was the thigh circumference in centimeters; and LBM was lean body mass in kilograms.

A validation procedure was done at 5 months when all measurements and runs were repeated, $\dot{V}O_2$/kg and $\dot{V}O_2$ were predicted, and $\dot{V}O_2$ and $\dot{V}O_2$/kg were measured. The prediction equation for $\dot{V}O_2$ accounted for 88% of the variance of the measured $\dot{V}O_2$ at 5 months with the SE of the estimate equal to 0.07 L/min (Fig 1). The variance of $\dot{V}O_2$ at 5 months accounted for by LBM, gender, and 2.4-run speed were 66%, 11%, and 4%, respectively. The prediction equation for $\dot{V}O_2$/kg accounted for 58% of the variance of measured $\dot{V}O_2$/kg at 5 months with the SE of the estimate equal to 27 mL of oxygen per kilogram of body weight per minute (Fig 2). We compared our equations for estimating oxygen uptake at 5 months with other authors' equations for estimating oxygen uptake in our subjects at 5 months (Tables 4 and 5). Male and female subjects are listed together and separately, because some authors generated equations for male and female subjects together and separately. Our equation to predict $\dot{V}O_2$ in the female subjects was a significant improvement over the other published equations. Otherwise, our determinations were comparable with those of other authors.

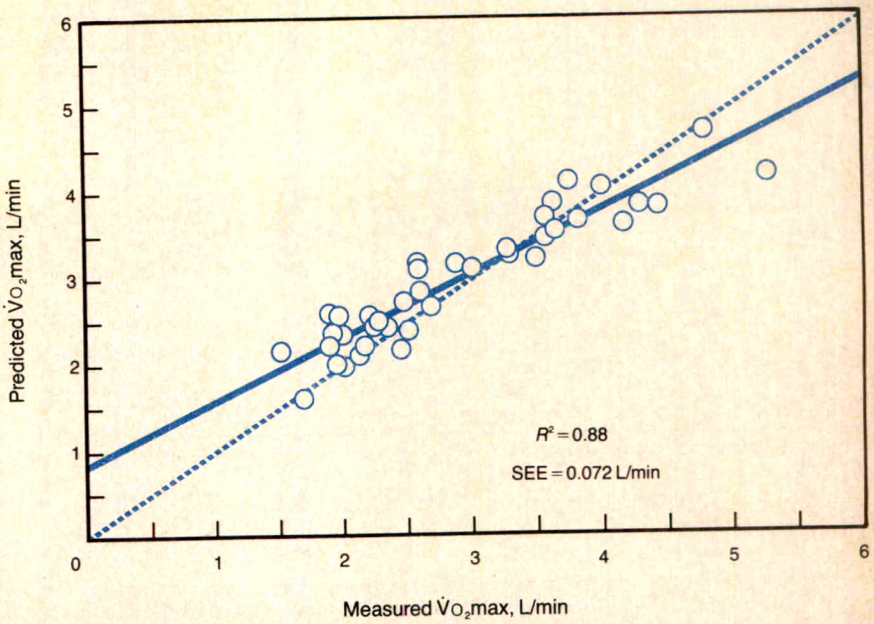


Fig 1.—Relationship between predicted maximum oxygen consumption ($\dot{V}O_2$max) (liters per minute) and measured $\dot{V}O_2$max (liters per minute) at the end of the study (n = 39). The dotted line represents the line of identity; the solid line, the regression line; and SEE, the SE of the estimate.

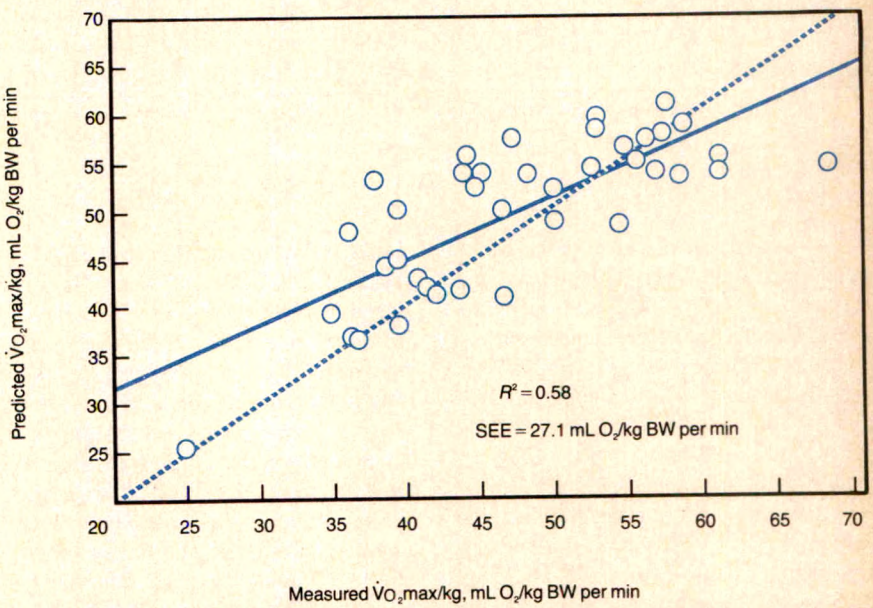


Fig 2.—Relationship between predicted maximum oxygen consumption ($\dot{V}O_2$max/kg) (milliliters per kilogram of body weight [BW] per minute) and measured $\dot{V}O_2$max/kg (milliliters per kilogram of body weight per minute) at the end of the study (n = 39). The dotted line represents the line of identity; the solid line, the regression line; and SEE, the SE of the estimate.

COMMENT

Our results document that $\dot{V}O_2$ can be predicted accurately in male and female adolescents. We have noted inaccuracies in the equations used by previous investigators as a result of the use of biased samples. One author used male subjects only,[18] two used competing athletes,[18,19] one investigator studied Japanese adolescents,[15] and another studied Norwegian adolescents.[16] These differences between study populations account for some of the inaccuracy of other equations in our female subjects.

Lean body mass accounted for the largest amount of variance in $\dot{V}O_2$, which is expected since maximal aerobic power is strongly related to LBM.[3(p3)] Predicting LBM and percent body fat from skin-fold measurements is imprecise.[23] Hydrostatic weighing or total body electrical conductivity measurements are more accurate but not practical for

Table 4.—Correlation Between Predicted Oxygen Consumption ($\dot{V}O_2$) and Measured $\dot{V}O_2$ at 5 Months in 39 Subjects in the Current Study Using the Authors' Equation Compared With Other Authors' Equations

	Other Authors' Original Studies*				Correlation With Current Study Subjects, *r*		
Author(s), y	n	Gender	Age, y	Predictor Variables	M and F	M	F
Present study	...	...	...	...	.92†	.93†	.87†
Matsui et al,[15] 1972	546	M, F	12-18	Weight	...	.86†	−.03
Andersen et al,[16] 1974	88	M	8-16	Weight/height or lean body mass	...	.95†	.58‡
	83	F	...	...	...	...	...
Klissouras,[17] 1973	50	M	7-13	Age, height, or weight	.77†	.88†	.01
Daniels and Olridge,[18] 1971	14	M	10-15	Age, height, weight	.83†	.90†	.17
Wells et al,[19] 1973	21	M, F	12-20	Lean body mass	...	.95§	−.03
McMiken,[20] 1976	Theoretical equation			Weight	.74§	...	...

*Refers to the number, gender, age range of the subjects, and variables used to predict $\dot{V}O_2$ by other authors in their original studies.
†$P<.0001$.
‡$P<.02$.
§$P<.01$.

Table 5.—Correlation Between Predicted Oxygen Consumption ($\dot{V}O_2$)/kg and Measured $\dot{V}O_2$/kg at 5 Months in 39 Subjects in the Current Study Using the Authors' Equation Compared With Other Authors' Equations

	Other Authors' Original Studies*				Correlation With Current Study Subjects, *r*		
Author(s), y	n	Gender	Age, y	Predictor Variables	M and F	M	F
Present study	...	...	...	...	.76†	.44‡	.84†
Cooper,[21] 1968	115	M	17-52	12-min run	.75†	.56§	.79§
Johnson et al,[22] 1979	150	M, F	18-25	12-min run	.75†	.56§	.79§

*Refers to the number, gender, age range of the subjects, and variables used to predict $\dot{V}O_2$ by other authors in their original studies.
†$P<.0001$.
‡$P<.01$.
§$P<.001$.

large-scale studies. Until these techniques are more accessible, using anthropometric techniques as an estimate of LBM and body fat will be necessary.

The 2.4-km run speed accounted for a significant but small amount of the variance of $\dot{V}O_2$, which is consistent with all other studies reviewed.[15-22]

Our equation for predicting $\dot{V}O_2$/kg was inaccurate and not acceptable. We reviewed studies of indirect methods of predicting $\dot{V}O_2$/kg in adolescents. They demonstrated significant correlations between $\dot{V}O_2$/kg and runs of varying distances and these correlations tended to improve as the length of the run and the heterogeneity of the sample increased.[4-9,24-26] However, they either did not predict $\dot{V}O_2$/kg accurately or did not generate an equation to predict $\dot{V}O_2$/kg.[4,5,22,27,28] Expressing oxygen uptake per body weight implies a constant and high correlation between $\dot{V}O_2$ and weight. In fact, the correlation is approximately .71.[29] The $\dot{V}O_2$ correlates better with LBM than body weight. Dividing $\dot{V}O_2$ by body weight simplifies the variability of LBM and body fat comprised by body weight, and has a different effect in an obese individual from a lean one. Therefore, $\dot{V}O_2$/kg of body weight may be harder to predict than $\dot{V}O_2$ from indirect measures, because the denominator is not a uniform entity. We conclude that it is difficult to predict $\dot{V}O_2$/kg accurately using indirect methods. To estimate $\dot{V}O_2$/kg for an adolescent, we suggest using our equation for $\dot{V}O_2$ and dividing by body weight.

This study is, to our knowledge, the first to assess the value of using estimated secondary sexual development in predicting $\dot{V}O_2$ and $\dot{V}O_2$/kg. Others have related skeletal age to submaximal work capacity and 12-minute run and found minimally significant or insignificant relationships.[30,31] Although the sexual maturity rating was related significantly to $\dot{V}O_2$, it also was correlated highly with LBM, making its contribution to the prediction of oxygen uptake, independent of LBM, a minimal one. There was no significant correlation between sexual maturity rating and $\dot{V}O_2$/kg. Sexual maturity ratings do not improve the prediction of oxygen uptake over that accounted for by LBM, gender, thigh circumference, and run performance in adolescents.

In summary, we have developed an equation for accurately estimating $\dot{V}O_2$ in adolescents, which is a significant improvement over other published equations, especially for female subjects. Our equation for predicting $\dot{V}O_2$/kg was inaccurate. An estimate of sexual maturity did not enhance the ability to predict $\dot{V}O_2$ or $\dot{V}O_2$/kg. The equation for predicting $\dot{V}O_2$ will be useful for estimating cardiovascular fitness in adolescents.

We thank Ron Saxon, Guy Roberts, Cathy Holman, and the administration, physical education staff, and students of Lakeside and Bush Schools and University Preparatory Academy, Seattle; Norma Womack and Michael Dixon for the preparation of the manuscript; William Klish, MD, and Claudia Kozinetz, PhD, for their review of the manuscript; and Pat Wilkens for her support.

References

1. Mitchell JH, Sproule BJ, Chapman CB. The physiological meaning of the maximal oxygen intake test. *J Clin Invest*. 1958;37:538-546.
2. Taylor HL, Buskirk E, Henschel A. Maximal oxygen intake as an objective measure of cardiorespiratory performance. *J Appl Physiol*. 1955; 8:73-80.
3. Bar-Or O. *Pediatric Sports Medicine for the Practitioner*. New York, NY: Springer-Verlag NY Inc; 1983.
4. Jackson AS, Coleman AE. Validation of distance run tests for elementary school children. *Res Q Exerc Sport*. 1976;47:86-94.
5. Maksud MG, Coutts KD. Application of the Cooper twelve-minute run-walk test to young males. *Res Q Am Assoc Health Phys Educ*. 1971;42:54-59.
6. Doolittle TL, Bigbee R. The twelve-minute run-walk: a test of cardiorespiratory fitness of adolescent boys. *Res Q Am Assoc Health Phys Educ*. 1968;39:491-495.
7. Metz KF, Alexander JF. An investigation of the relationship between maximum aerobic work capacity and physical fitness in twelve to fifteen year-old boys. *Res Q Exerc Sport*. 1970;41:75-81.
8. Gutin B, Fogle RK, Stewart K. Relationship among submaximal heart rate, aerobic power, and running performance in children. *Res Q Exerc Sport*. 1976;47:536-539.
9. Olree H, Stevens C, Nelson T, Agnevik C, Clark RT. Evaluation of the AAHPER youth fitness test. *J Sports Med Phys Fitness*. 1965;5:67-71.
10. Hollingshead AB. *Two Factor Index of Social Position*. New Haven, Conn: privately printed; 1965.
11. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics*. 1980;66:918-920.
12. Parizkova J. Total body fat and skinfold thickness in children. *Metabolism*. 1961;10:794-807.
13. Siri WE. Body composition from fluid spaces and density. In: Borzek J, Henschel A, eds. *Techniques for Measuring Body Composition*. Washington, DC: National Academy of Sciences; 1961:223-224.
14. Pate RR, Blair SN. Exercise and the prevention of atherosclerosis: pediatric complications. In: Strong WB, ed. *Atherosclerosis: Its Pediatric Aspects*. New York, NY: Grune & Stratton; 1978:13.
15. Matsui H, Miyashita M, Miura M, Kobayashi K, Hoshikawa T, Kamei S. Maximum oxygen intake and its relationship to body weight in Japanese adolescents. *Med Sci Sports Exerc*. 1972;4:27-32.
16. Andersen KL, Seliger V, Rutenfranz J, Mocellin R. Physical performance capacity of children in Norway. Part I. *Eur J Appl Physiol*. 1974;33:177-195.
17. Klissouras V. Prediction of potential performance with special reference to heredity. *J Sports Med Phys Fitness*. 1973;13:100-107.
18. Daniels J, Olridge N. Changes in oxygen consumption of young boys during growth and running training. *Med Sci Sports Exerc*. 1971;3:161-165.
19. Wells CL, Scrutton EW, Archibald LD, Cooke WP, De La Mothe JW. Physical working capacity and maximal oxygen uptake of teenaged athletes. *Med Sci Sports Exerc*. 1973;5:232-241.
20. McMiken DF. Maximal aerobic power and physical dimensions of children. *Ann Hum Biol*. 1976;3:141-147.
21. Cooper KH. A means of assessing maximal oxygen intake. *JAMA*. 1968;203:201-204.
22. Johnson DJ, Oliver RA, Terry JW. Regression equation for prediction of performance in the twelve-minute run-walk test. *J Sports Med Phys Fitness*. 1979;19:165-170.
23. Forbes GB. *Human Body Composition: Growth, Aging, Nutrition, and Activity*. New York, NY: Springer-Verlag NY Inc; 1987:72-85.
24. Krahenbuhl GS, Pangrazi RP, Petersen GW, Burkett LN, Schneider MJ. Field testing of cardiorespiratory fitness in primary school children. *Med Sci Sports Exerc*. 1978;10:208-213.
25. Krahenbuhl GS, Pangrazi RP, Burkett LN, Schneider MJ, Peterson G. Field estimation of $\dot{V}O_2$max in children eight years of age. *Med Sci Sports Exerc*. 1977;9:37-40.
26. Disch J, Frankiewicz R, Jackson A. Construct validation of distance run tests. *Res Q Am Assoc Health Phys Educ*. 1975;46:169-176.
27. Davies CTM, Barnes C, Godfrey S. Body composition and maximal exercise performance in children. *Hum Biol*. 1972;44:195-214.
28. Woynarowska B. The validity of indirect estimations of maximal oxygen uptake in children 11-12 years of age. *Eur J Appl Physiol*. 1980;43:19-23.
29. Katch V. Use of the oxygen/body weight ratio in correlation analysis: spurious correlations and statistical correlations. *Med Sci Sports Exerc*. 1973;5:253-257.
30. Bouchard C, Malina RM, Hollmann W, Leblanc C. Relationships between skeletal maturity and submaximal working capacity in boys 8 to 18 years. *Med Sci Sports Exerc*. 1976;8:186-190.
31. Kemper HC, Versehuer R. Relationship between biological age, habitual physical activity, and morphological psychological characteristics of 12 and 13 year old boys. *Acta Paediatr Belg*. 1974; 28:191-203.

Editorial Trivia

Shortest title for a scientific paper: "!"

Longest title: 45 words

Longest word in a title: "Rauchgasentschwefelungsanlagen" (definition: flue gas desulfurization)

Most alliterative title: "Turning Transducer Triggers Technique to Tackle Transformed Torque" (The same author also had a paper entitled: "Layering Leisurely Liquids Leaves Linear Laminar Flow Languishing in Line")

Shortest abstract: "No" (The title was a question)

Longest mathematical formula: 16 pages

Longest editorial delay on record: 26 years 5 months (Received April 1960, published in September 1986 in the *Bulletin of the JSME* in Japan)

Mike Collins, *Inspec*
cited in *Science* (1988;242:1130)

Experience With a Metered-Dose Inhaler With a Spacer in the Pediatric Emergency Department

Grey Benton, RRT, MA; Randolph C. Thomas, MD; Bruce G. Nickerson, MD; John C. McQuitty, MD; Jerry Okikawa, RRT, MBA

• Studies of adults suggest that metered-dose inhalers with spacers are as effective as hand-held nebulizers for bronchodilator delivery. We studied 13 children with acute asthma. They received two puffs every 2 minutes from metered-dose inhalers with spacers (range, 4 to 14 puffs) titrated until improvement stopped. Peak expiratory flow increased 34% for metered-dose inhalers with spacers after the first 2 puffs and increased 87% for metered-dose inhalers with spacers after dose titration. After titration, respiratory rate decreased by 12%, heart rate increased by 2%, and breath sounds improved in 92% of the patients. We concluded that the metered-dose inhalers with spacers are an effective device for the treatment of asthma in the pediatric emergency department and that the use of metered-dose inhalers with spacers with titration can achieve significant bronchodilation in the treatment of patients with acute asthma.

***(AJDC.* 1989;143:678-681)**

Studies in adults suggest that a metered-dose inhaler with a spacer (MDIS) can deliver inhaled bronchodilators to the lungs as effectively as a gas-powered hand-held nebulizer (HHN).[1-10] In addition, the MDIS takes less of the therapist's time and costs less (per treatment) than the HHN.[3,8,10,11] These factors along with the increasing need for cost-effective, efficacious medical care led us to examine our provision of bronchodilators in the emergency department. In this study we examined albuterol sulfate delivery by MDIS in patients with moderate asthma presenting to our emergency department. The administered dose was titrated to optimize therapeutic response.

Accepted for publication January 9, 1989.

From the Childrens Hospital Medical Center, Oakland, Calif.

The abstract of this article was presented in part at the 28th Annual Meeting of the Ambulatory Pediatric Association, May 3, 1988, Washington, DC.

Reprint requests to Pulmonary Function Laboratory, Childrens Hospital Medical Center, 747 52nd St, Oakland, CA 94609 (Dr Nickerson).

PATIENTS AND METHODS

Thirteen patients were studied from August through November 1987, using a regimen that was already in use in our hospital. Patients with moderate asthma entered the study as they presented to the emergency department if their parents consented and they were able to perform the peak expiratory flow (PEF) maneuver. Adults and cyanotic patients were excluded.

The inhaled dose was titrated by measuring the PEF with a peak flow meter, giving two puffs of albuterol sulfate in sequence with the MDIS, auscultating breath sounds, and then measuring the PEF and auscultating the breath sounds again. The process was repeated until wheezes, aeration, and PEF did not improve. The average patient required 8 ± 3 (mean ± SD) puffs (range, 4 to 14) at an interval of 2 ± 2 minutes per puff (range, 1 to 13 years). The MDIS equipment consisted of an inhaler (Proventil, Schering Corp, Kenilworth, NJ) attached to a spacer (Aerochamber, Monaghan, Plattsburg, NY).

Patient Population

All patients were known asthmatics with an acute exacerbation at home. Before the emergency department visit, 62% of the patients were taking oral anhydrous theophylline, 39% were using an inhaled sympathomimetic bronchodilator, 31% were using oral theophylline and an inhaled bronchodilator, and 8% were taking prednisone. By history, 31% were not taking their prescribed medications. In our study population, 85% of patients were male. The average age (± SD) was 9 ± 3 years (range, 5 to 15 years).

Calculations

Breath sound improvement data represented the percent of the time that an improvement was recorded in the chart by the emergency department physician. This was calculated by dividing the number of times breath sound improvement was noted by the number of times breath sounds were recorded.

The data used to calculate results included pretreatment data and posttreatment data. With the exception of the PEF after two puffs, data collected between MDIS puffs was used only for dose titration.

For comparative purposes, HHN treatment data were sampled from the medical records of known asthmatics. Twenty-five records were selected and the data were averaged to provide a baseline group for comparison. Only initial emergency department treatments using saline-diluted albuterol were selected. The MDIS and HHN data were then compared using the unpaired Student t test ($P = .05$). Data are reported as mean ± SD.

RESULTS

Initial PEF was 144 ± 70 L/min for the MDIS group compared with 173 ± 62 for the HHN data. Peak expiratory flow increased 87% ± 104% (range, 14% to 412%) for MDIS at the end of titration compared with 40% ± 38% (range, 0% to 119%) for the HHN data. The PEF of the MDIS group increased 34% ± 22% (range, 10% to 88%) after the first two puffs (the dose equivalent of an HHN treatment). Heart rate increased 2% ± 12% (range, −17% to +27%) for MDIS compared with an increase of 8% ± 4% (range, +2% to +14%) for the HHN data.

Respiratory rate decreased 12% ± 26% (range, −39% to +42%) for MDIS data compared with an increase of 15% ± 25% (range, −18 to +58%) for HHN data. Breath sound improvement occurred in 92% of the patients who used an MDIS and in 87% of the patients who used an HHN.

The mean dose of albuterol sulfate administered to the MDIS group was 6 ± 2 μg/kg after two puffs and 23 ± 12 μg/kg after titration. The mean dose

administered to the HHN group was 104 ± 28 μg/kg. No patient experienced side effects requiring withdrawal from the study. The results are summarized in Tables 1 through 3.

COMMENT

The purpose of this study was to examine MDIS as a means to deliver albuterol to asthmatic children in the emergency department. Titration was added to optimize drug delivery. Currently, the majority of our patients are treated with an HHN driven by compressed gas and containing medication that has been diluted with saline.

The following factors influenced our choice of MDIS: (1) Many patients are familiar with the MDIS from use at home or in the hospital. If patients are not already familiar with MDIS, some benefit may be gained by familiarizing them with this form of therapy. (2) Recent literature indicates equal efficacy between the HHN and the MDIS.[1-10] (3) The MDIS can be used in most settings because no external gas source is needed.[10] (4) The MDIS can be used immediately with very little preparation. (5) The MDIS treatment takes less time. (6) Treatment effect can be titrated more easily with the MDIS. (7) An MDIS costs less because therapist time is reduced.[3,10,11] (8) The MDIS delivers less drug to the patient than the HHN (for a similar level of bronchodilation). (9) The patient can be given the MDIS for future home use.

We examined the literature regarding metered-dose inhalers and freon toxicity[9,12-17] and concluded that the risk to the patient would be minimal if the following guidelines were used: (1) no more than two puffs at a time before patient reevaluation; (2) puff-to-puff waiting time of at least 1 minute; (3) an absolute ceiling of 20 puffs in any treatment period (Twenty puffs would represent a maximum dose of 350 mL of freon over 20 minutes. For a 5-year-old child this should represent less than 3% of the minute volume.); and (4) direct medical supervision is advised.

The literature that we examined did not suggest a significant risk of freon toxicity for patients using an MDIS under this protocol. The half-life of the propellants is short. Not all of the freon

Table 1.—Hand-Held Nebulizer (HHN) and Metered-Dose Inhaler (MDI)/Spacer Results*

Variable	MDI/Spacer Mean	MDI/Spacer SD	HHN Mean	HHN SD	Significant Difference?
Initial PEF, L/min	144	70	173	62	No
Initial % predicted PEF	48	19	54	20	No
% Change after 2 puffs	+34	22	...	...	...
Overall % change in PEF	+87	104	+40	38	No
Total dose, μg/kg	23	12	104	28	Yes
Heart rate change, %	+2	12	+8	4	No
Respiratory rate change, %	−12	26	+15	25	Yes
Breath sound improvement, %	87	...	92	...	No
Adverse side effects	None	...	None	...	...
No. of patients	13	...	25	...	...

*PEF indicates peaked expiratory flow.

Table 2.—Data for Patients Treated With The Metered-Dose Inhaler (MDI)/Spacer Combination and Hand-Held Nebulizer*

	Age, y	Weight, kg	PEF Before Treatment, L/min	Predicted PEF Before Treatment, L/min	Change After 2 Puffs, %	Total No. of Puffs	Final Change, %	Administered Dose, μg/kg
MDI/Spacer Combination Data								
	5	21	80	44	38	9	50	39
	6	24	100	41	30	14	115	52
	6	28	90	39	33	8	67	26
	7	27	60	24	25	6	125	20
	8	24	105	44	14	8	24	30
	8	27	205	75	24	6	32	20
	8	38	100	31	50	9	105	22
	9	36	185	56	14	8	35	20
	11	39	220	63	27	6	55	14
	12	34	250	79	10	4	14	11
	12	45	130	42	54	6	62	12
	12	45	260	69	...	8	33	16
	15	72	85	17	88	14	412	18
Mean (SD)	9 (3)	35 (14)	144 (70)	48 (19)	34 (22)	8 (3)	87 (104)	23 (12)
Hand-Held Nebulizer Treatment Data†								
Mean (SD)	11 (4)	39 (12)	173 (62)	54 (20)	...	4 (1)	40 (38)	104 (28)

*PEF indicates peaked expiratory flow. The only significant ($P = .05$) differences between groups were in age and administered doses.
†See Table 3.

Table 3.—Historical Data for Hand-Held Nebulizer Treatments*

Age, y	Weight, kg	PEF Before Treatment, L/min	% Predicted PEF Before Treatment, L/min	Administered Dose, mg	Final Change, %	Administered Dose, μg/kg
3	16	...	...	1	...	65
4	17	...	...	2	...	118
5	22	105	50	3	119	136
6	24	215	88	3	0	123
6	28	...	...	3	...	107
9	24	130	54	3	8	127
9	36	245	75	3	22	84
11	42	110	37	6	64	144
11	...	105	28	5	38	...
12	45	...	...	3	...	67
13	43	...	...	5	...	105
13	38	170	41	3	24	79
13	42	...	...	4	...	96
13	43	...	...	4	...	93
13	43	...	...	4	...	93
14	36	...	...	7	...	192
14	51	...	...	5	...	99
14	50	...	...	5	...	100
14	50	...	...	5	...	100
14	40	...	...	4	...	101
14	49	...	...	4	...	82
14	50	...	...	5	...	100
15	56	250	60	4	48	71
15	49	...	...	5	...	102
15	50	230	...	5	...	100
Mean (SD) 11 (4)	39 (12)	173 (62)	54 (20)	4 (1)	40 (38)	104 (28)

*PEF indicates peaked expiratory flow.

is absorbed and most is exhaled within a few minutes. Dollery et al[16] found that a patient would have to take a puff on every breath for 12 to 24 puffs to achieve a potentially hazardous blood level. Our protocol spread this dose over 1 minute per breath so that there was ample time for excretion.

We established safety limits for the MDIS before the study. We based the 20-puff limit on the ratio of oral to MDI doses (22 puffs delivers the same amount of medication as a 2-mg oral dose). This safety margin is further widened by the fact that the majority of the inhaled bronchodilator contents will be exhaled.[4,9,12] In addition, the elevated inspiratory flow rates typical with exacerbations of asthma cause increased impaction losses of aerosol particles in the throat. This further lowers the dose that reaches the lungs.

Our decision to use titration was reinforced by studies that have used up to eight breaths from an MDIS without adverse side effects.[1,2,18] Our reasoning was that the high inspiratory flow rates of asthmatics with exacerbation would lead to significant drug losses by particle impaction on the back of the throat. We felt that dose titration would compensate for the loss of drug.

We did not experience treatment failures in the small number of patients studied. Dyspnea did not increase with any patient. Side effects were uncommon with both groups. We acknowledge that albuterol is not approved by the Food and Drug Administration for use in children less than 12 years old or for use more than four times per day by either MDIS or HHN. However, there is extensive experience with use in children from many institutions.

The MDI and HHN treatments differed in the following ways: (1) Oxygen is used with the HHN and is not used with the MDIS. This was a theoretical concern, but none of these patients with moderate asthma experienced cyanosis with MDIS treatments. (2) Oral inhalation with the MDIS and oral or nasal breathing with the HHN. (3) Greater ventilatory dead space with the HHN mask. (4) The patients treated with an MDIS were studied from August through November 1987, while the HHN group was collected between April 1987 and October 1988. Thus, differences due to seasonal allergens or infectious triggers cannot be excluded.

The spacer used with the MDIS has a mouthpiece; therefore, patients using the MDIS inhaled through their mouths. By contrast, HHN users usually breath through their noses.

Patients using the inhaler were coached to inhale slowly and hold their breath for several seconds. Patient compliance varied greatly with the patient's level of dyspnea. Most MDIS patients made a substantial effort to perform the requested breathing patterns. Even without full compliance, any reduction in inspiratory flow or increase in depth may enhance aerosol deposition in the lungs.[9,19,20] Patients using an HHN may increase their depth of ventilation because the mask adds a small amount of ventilatory dead space. Overall, patients using an MDIS may have delivered medication to the lower airways more effectively than patients using an HHN.

We did not use supplemental oxygen in these patients with moderate asthma. Cyanotic patients were excluded from the study and no patients became cyanotic during the study.

The literature suggests that both treatments are similar with respect to aerosol particle size,[12] particle distribution in the lungs, percent deposition in the lungs,[12] and bronchodilation. We therefore expected both groups of patients to benefit equally from their treatments. With the protocol that we used, it would appear that the MDIS is equivalent to the HHN after two puffs. Further improvement in the PEF occurs with titration; however, the final PEF for the MDIS was not significantly different from the final PEF for the HHN data. The MDIS PEF after titration was significantly greater than the

PEF after two puffs. The heart rate changes seen with the titrated MDIS did not differ significantly from those in the HHN data. In both cases, the heart rate increased slightly.

The respiratory rate fell for the MDI-treated patients and rose in the HHN data. This difference is significant and indicates that the MDI may do more to lower the respiratory rate than the HHN. It is also possible that the stress of breathing through the mask, the mask's dead space, airway stimulation by the aerosol, or some other factor kept the respiratory rate elevated in the HHN data. In fact, it has been our experience that the respiratory rate usually does not fall during aerosol treatment by an HHN. Further study would be required to validate this observation.

Breath sounds improved more often in the MDI group than in the HHN data; however, the difference was not significant. We feel that the simple nature of the evaluation method for this factor minimized subjective bias. The observer simply noted improvement or lack of improvement. We did this to avoid the pitfalls of scoring systems that may be applied differently by different individuals.

There was a significant difference between the mean doses used in this study and the mean dose from the HHN data. The ratio between the dose at two puffs and the HHN dose was 1 to 18 and the ratio between the titrated dose and the HHN was 1 to 4.5. This indicates that 4.5 to 18 times more drug is needed when an HHN is used vs when an MDIS is used.

CONCLUSION

We conclude that the MDIS is an effective device for the treatment of asthma in the pediatric emergency department and that the MDIS with titration can achieve significant bronchodilation in the treatment of patients with acute asthma.

This study was supported by the Departments of Pulmonary Medicine and Emergency Medicine at Childrens Hospital Medical Center, Oakland, Calif.

References

1. Tarala RA, Madsen BW, Paterson JW. Comparative efficacy of salbutamol by pressurized aerosol and wet nebulizer in acute asthma. *Br J Clin Pharmacol*. 1980;10:393-397.
2. Harrison BA, Pierce RJ. Comparison of wet and dry aerosol salbutamol. *Aust NZ J Med*. 1983;13:29-33.
3. Jasper AC, Mohsenifar Z, Kahan S, Goldberg HS, Koerner SK. Cost-benefit comparison of aerosol bronchodilator delivery methods in hospitalized patients. *Chest*. 1987;91:614-618.
4. Cushley MJ, Lewis RA, Tattersfield AE. Comparison of three techniques of inhalation on the airway response to terbutaline. *Thorax*. 1983; 38:908-913.
5. Salzman GA, Steele M, Elenbaas R. A comparison of two delivery methods for aerosolized metaproterenol in the treatment of asthmatics in the emergency room. *Chest*. 1987;92(suppl):123S.
6. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a meter dose inhaler in stable chronic air flow limitation. *Chest*. 1977;91:804-807.
7. Christenson P, Arborelius M, Lilja B. Salbutamol inhalation in chronic asthma bronchiale: dose aerosol vs jet nebulizer. *Chest*. 1981;79:416-419.
8. Cissik JH, Bode FR, Smith JA. Double-blind crossover study of five bronchodilator medications and two delivery methods in stable asthma. *Chest*. 1986;90:489-493.
9. Newhouse MT, Dolovich MB. Control of asthma by aerosols. *N Engl J Med*. 1986;315:870-874.
10. Turner JR, Corkery KJ, Eckman D, Gelb AM, Lipavsky MA, Sheppard D. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. *Chest*. 1988; 93:476-481.
11. Berenberg MJ, Baigelman W, Cupples LA, Pearce L. Comparison of metered-dose inhaler attached to an aerochamber with an updraft nebulizer for the administration of metaproterenol in hospitalized patients. *J Asthma*. 1985;22:87-92.
12. Newman, SP. Therapeutic inhalation agents and devices: effectiveness in asthma and bronchitis. *Inhalation Ther*. 1984;76:194-207.
13. Clark DG, Tinston DJ. Cardiac effects of isoproterenol, hypoxia, hypercapnia and fluorocarbon propellants and their use in asthma inhalers. *Ann Allergy*. 1972;30:536-541.
14. Tobin MJ. Use of bronchodilator aerosols. *Arch Intern Med*. 1985;145:1659-1663.
15. Dollery CT, Draffen GH, Davies DS, Williams FM, Conolly ME. Blood concentrations in man of fluorinated hydrocarbons after inhalation of pressurized aerosols. *Lancet*. 1970;1:1164-1166.
16. Dollery CT, Williams FM, Draffan GH, et al. Arterial blood levels of fluorocarbons in asthmatic patients following use of pressurized aerosols. *Clin Pharmacol Ther*. 1970;15:59-66.
17. Paterson JW, Sudlow MF, Walker SR. Blood-levels of fluorinated hydrocarbons in asthmatic patients after inhalation of pressurized aerosols. *Lancet*. 1971;2:565-568.
18. Spector SL, Gomez MG. Dose-response effects of albuterol aerosol compared with isoproterenol and placebo aerosols. *J Allergy Clin Immunol*. 1977;59:280-286.
19. Pavia D, Thompson ML, Clarke SW, et al. Effect of lung function and mode of inhalation of penetration of aerosol into the human lung. *Thorax*. 1977;32:194-197.
20. Lawford P, McKenzie D. Pressurized aerosol inhaler technique: how important are inhalation from residual volume, inspiratory flow rate and the time interval between puffs? *Br J Dis Chest*. 1983;77:276-281.

AJDC Has Moved . . .

The AJDC editorial office is now located at Tulane University. Please address all correspondence, manuscripts, and inquiries to Vincent A. Fulginiti, MD, Editor, *AJDC*, Dean's Office, Room 1529, Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112; (504) 584-1989.

The Ameliorating Effect of Lumbar Puncture in Viral Meningitis

M. Jaffe, MB, BCh, MRCP(Edin), DCH; I. Srugo, MD; E. Tirosh, MD; A. A. Colin, MD; Y. Tal, MD

• To test the hypothesis that lumbar puncture in viral meningitis results in symptomatic improvement, a group of 48 children was studied. Twenty-six patients had proved aseptic meningitis, and 22 had infections outside the central nervous system. Before and after lumbar puncture each subject was repeatedly scored for symptoms independently by the attending pediatrician and a parent. Marked symptomatic improvement in children with meningitis was demonstrated following lumbar puncture, while no significant change was demonstrated in the control group. The mechanism underlying this improvement is not clear; however, we consider a number of possible explanations.

(*AJDC*. 1989;143:682-685)

Lumbar puncture (LP) is a frequently performed procedure in the hospital emergency department. Headache following LP is a well-documented phenomenon and is probably due to a cerebrospinal fluid (CSF) leak through the dura mater, resulting in a fall of CSF pressure.[1-4] It has been our observation, however, that the symptoms of many patients with viral meningitis seem to improve dramatically after LP. A survey of the literature failed to reveal any reference to this observation, and this study was planned to systematically evaluate the symptomatic effect of LP in viral meningitis.

PATIENTS AND METHODS

The study group comprised all children between the ages of 6 months and 12 years who were examined in the emergency department with clinically suspected meningitis. The diagnosis was based on one or more of the following criteria: fever, malaise, vomiting, headache, and signs of meningeal irritation. All children who had received antibiotic treatment prior to LP were excluded from the study, as were those who were eventually proved to suffer from bacterial meningitis. During the 4-hour observation, the patients received no intravenous or analgesic therapy.

Population

Forty-nine children, 28 of whom were boys, were studied. The mean age was 48 months. Twenty-four children (49%) were 3 years of age or older. Written parental informed consent was obtained before participation in the study.

Viral meningitis was diagnosed in 26 children on the basis of the following CSF criteria: more than 6×10^6 lymphocytes per liter, glucose levels at least two thirds as high as the blood glucose levels, a negative direct smear and culture, and a spontaneous clinical recovery within a few days. A variety of infections not involving the central nervous system were diagnosed in 22 children with normal CSF findings, and this was the control group. One child with bacterial meningitis was excluded from the study.

Procedure

Parents were asked to complete a nine-item questionnaire (Table 1). The first five items were derived from a "toxicity index" score,[5] and the remaining four items were used by the investigators on the basis of clinical experience.

Each item was assigned a severity score of 1 to 3. A score of 3 represented the most marked manifestation of an item, while a score of 1 represented the mildest manifestation (Table 2). Parents were instructed to ignore items that were irrelevant to their child.

The admitting pediatrician simultaneously completed a questionnaire identical to the parents' questionnaire with four additional items deemed relevant in this setting (Tables 2 and 3).

Immediately following the completion of the questionnaire, while in the sitting position, the child underwent an LP performed by an experienced pediatrician. Five milliliters of CSF were withdrawn for routine biochemical, microscopic, and bacteriologic analysis.

The parents and pediatricians independently completed the same questionnaire five more times 10, 30, 60, 120, and 240 minutes following the LP. All participants were unaware of the CSF results, which were communicated to another attending pediatrician.

The questionnaires were stored for later analysis. The ultimate "severity score" was derived from the following equation: (total points in the severity score of the items answered × 100)/maximal possible score for the answered items.

Interobserver agreement was assessed before the study by comparing the scores assigned by each of the four participating pediatricians with scores assigned by one reference pediatrician. This test was done for 20 ill, febrile children suffering from a variety of infections, including meningitis. The correlation coefficient was calculated as 0.95 (range, 0.92 to 0.97).

A paired Student t test to compare the means at 0 and 60 minutes was used for statistical analysis. Analysis of variance was not feasible because not all of the parents completed the full questionnaire following LP.

RESULTS

Viral meningitis was diagnosed in 26 children. The LP in 22 children was normal, and their eventual diagnoses were as follows: 16 had upper-respiratory-tract infections, 4 had acute otitis media, and 2 had gastroenteritis.

The mean severity score of all patients before and after LP is given in Table 4. The mean severity scores of the parents and pediatricians before and after LP revealed no statistically significant differences (Tables 4 and 5). Following LP, the subjects suffering from viral meningitis demonstrated a marked improvement, which was reflected by both the pediatrician and parent severity scores. This was in contrast to the insignificant improvement in the

Accepted for publication December 12, 1988.

From the Department of Pediatrics, Haifa Medical Center, and the Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

Reprints not available.

Table 1.—Parent Severity Scores for 26 Patients With Viral Meningitis

Item	Mean Parent Severity Scores*								
	<3 y of Age			≥3 y of Age			Total		
	Before LP	60 min After LP	Difference, %	Before LP	60 min After LP	Difference, %	Before LP	60 min After LP	Difference, %
Quality of cry	64	63	1.6	54	48	11	57	53	7
Skin color	61	41	33	55	46	16	57	43	25
Reaction to touch	58	42	28	58	50	14	55	45	18
Reaction to voice	69	56	19	62	52	16	65	53	18
Vomiting	55	33	40	59	33	44	57	33	42
Drinking	64	67	−5	64	47	27	67	57	15
Talking	79	54	32	57	45	21	69	49	29
Headache	53	53	0	81	50	38	56	47	16
General condition	67	41	39	52	55	−6	58	47	19

*LP indicates lumbar puncture.

control group. Sixty minutes after LP, the mean improvement in the parent score was 29%, and the mean pediatrician score improved by 39%. Twenty-one of 26 children suffering from viral meningitis had a maximal improvement in either the parent or pediatrician score of 30% or more. In contrast, 60 minutes after LP, the control group had a mean improvement of only 8% in the parent score and 7.5% in the pediatrician score. Only 4 of 22 children in the control group had a maximal improvement of 30% or more. The difference between the two groups is statistically highly significant ($z=4.3$, $P<.0001$). The effect of age on the improvement in the severity score of the 26 children with viral meningitis is seen in Table 5. The mean change in the status of the group below 3 years old after LP was not significantly different from that of the older subjects. Similarly, no difference was found related to the sex of the patients.

Each item of the questionnaire was separately analyzed before and 60 minutes after LP (Tables 1 and 3). The items were divided into three groups according to the degree of improvement following LP. The highest score (pediatrician or parent) was considered. The total range of improvement was 0% to 44%; therefore, three groups were arbitrarily defined. Improvement up to 15% was defined as "mild," 16% to 30% as "moderate," and more than 30% as "marked."

Mild improvement was found only for the "quality of cry." Moderate improvement was found for skin color, reaction

Table 2.—Details of Pediatrician's Questionnaire

Item	Score		
	1	2	3
Quality of cry	Strong, spontaneous cry	Weak, whining cry	High-pitched cry
Skin color	Pink, healthy-looking	Pale	Cyanotic or gray
Reaction to light touch on limb with parent's hand	Immediate withdrawal of limb and/or cry	Sluggish withdrawal and/or short cry	No reaction
Reaction to conversational voice (1-m distance)	Immediate reaction (smile or verbalization)	Reaction difficult to obtain/transient alerting response (social or vocal)	No response
History of vomiting during 2 h before examination	No vomiting	1 or 2 vomits	>2 vomits
Drinking water offered by parent	Free drinking	1 or 2 sips	Refusal to drink
Talking	Spontaneous conversation	Short responses to questions	No verbalization
History of headache	No headache	Mild complaint	Repeated complaint
General condition	Looks healthy	Looks mildly sick	Looks very sick
Nausea at food offered by parents	No nausea	Mild expression of nausea	Retching at offered food
Photophobia (bright sunlight or flashlight 1 m from face)	No photophobia	Mild photophobia	Severe photophobia
Eating food of choice offered by parent	Normal appetite	Small sample of food ingested	Refusal to eat
Other spontaneous complaint of pain (when old enough to verbalize)	None	Mild complaint	Repeated complaint

Table 3.—Pediatrician Severity Scores for 26 Patients With Viral Meningitis

Item	Mean Pediatrician Severity Scores*								
	<3 y of Age			≥3 y of Age			Total		
	Before LP	60 min After LP	Difference, %	Before LP	60 min After LP	Difference, %	Before LP	60 min After LP	Difference, %
Quality of cry	57	40	30	42	37	12	43	40	7
Skin color	48	42	13	40	38	5	44	38	14
Reaction to touch	61	36	41	47	33	30	54	37	31
Reaction to voice	79	45	43	52	36	31	67	42	37
Vomiting	55	33	40	58	33	43	58	33	43
Drinking	63	45	29	58	47	19	59	48	19
Talking	80	50	38	56	45	20	65	50	23
Headache	67	38	43	90	48	47	81	39	52
General condition	85	50	41	69	47	32	76	52	33
Nausea	50	40	20	52	36	31	50	37	26
Photophobia	47	42	11	53	36	32	52	37	29
Eating	80	61	24	69	49	29	72	55	24
Other pain	46	37	20	59	38	36	52	37	29

*LP indicates lumbar puncture.

Table 4.—Severity Scores for All Patients Before and After Lumbar Puncture

Time, min	Patients With Viral Meningitis (n=26)				Controls (n=22)			
	Mean Parent Score	% Change	Mean Pediatrician Score	% Change	Mean Parent Score	% Change	Mean Pediatrician Score	% Change
0	63.8	. . .	61.5	. . .	57.6	. . .	53.2	. . .
10	54.9	14	51.1	17	54.3	6	50.3	5.5
30	46.5	27	40.7	34	53.4	7	50.4	5
60	45.4*	29	37.6*	39	53.1†	8	49.2†	7.5
120	41.6	35	36.8	40	53	8	49.1	7.5
240	41.6	35	36.7	40	53	8	49.1	7.5

*$P<.001$.
†Not significant.

to touch, reaction to voice, eating, and drinking. Marked improvement was found for headache, vomiting, and general condition.

Some differences between the pediatrician and parent scores were noted, but in general there was a marked similarity between the two sets of observations (Tables 1 and 3).

In patients below 3 years of age, marked improvement was noted in the clinical criteria of quality of cry, skin color, reaction to touch, reaction to voice, and general condition. In the older patients the main improvement was in headache and nausea, symptoms that older children are more able to express.

Table 5.—Severity Scores for 26 Children With Viral Meningitis Correlated With Age

	Mean Parent Severity Score		Mean Pediatrician Severity Score	
	Age <3 y, (n=10)	Age ≥3 y, (n=16)	Age <3 y, (n=10)	Age ≥3 y, (n=16)
Before lumbar puncture	66	60	64	57
60 min after lumbar puncture	46	43	40	36
% change	30	28	37.5	37

COMMENT

This study conclusively verifies the clinical impression of improvement in children undergoing LP for viral meningitis. A less-marked alleviation of certain symptoms also occurred in a control group of febrile children with infections outside the central nervous system; these changes, however, were not statistically significant. A control group consisting of patients with suspected meningitis whose LP was delayed for a few hours of observation would have been of scientific interest, but for obvious ethical reasons this was not feasible.

On analysis of the individual items, it was found that headache and vomiting showed the most marked improvement. In the older children, who were able to verbalize, the alleviation of headache was most impressive. It was not possi-

ble to assess headache in the very young.

Phenomena of a more general nature, such as quality of cry, skin color, reaction to touch, reaction to voice, and desire for liquid and food, also showed improvement, but the changes were less marked.

The most likely explanation for the improvement, especially with regard to headache and vomiting, is a decrease in CSF pressure following LP. This speculation is difficult to prove, for although increased CSF pressure has been documented in bacterial meningitis,[6,7] this is not the case in viral meningitis. Of our nine patients with open fontanelles, none showed any bulging, and no ophthalmologic evidence of increased intracranial pressure (ICP) was found. These signs are not highly sensitive for a mild increase in ICP, and therefore they do not necessarily exclude this possibility.

Removal of 5 mL of CSF constitutes 5% to 10% of the total CSF volume.[8,9] The change in the ICP as a result of a change in the CSF volume depends on the "intracranial elastance" or the pressure-volume relationship.[10,11] Within the normal range of ICP values, the pressure-volume curve increases gradually, but at a certain threshold the brain tissue compliance decreases and the curve becomes steeper. Therefore, small CSF volume increments will result in a disproportionate increase in the ICP. This phenomenon is even more marked in children, since their compliance is lower than that of adults.[12] In children with shunts for hydrocephalus, this threshold ranges between 10 and 25 mm Hg,[11] and beyond this point the addition or removal of only 2 mL of fluid results in a significant change in the ICP. It is unlikely that any of our patients reached this threshold, and, therefore, it is unlikely that a marked decrease in the ICP occurred. Moreover, the rate of CSF formation is about 20 mL/h,[8,9] and it is independent of ICP[9,13] and age.[9,14] The 5-mL withdrawal of CSF would therefore have been replenished within about 15 minutes. In our study the clinical improvement lasted for at least 4 hours. The increased ICP hypothesis for headaches is only tenable if one assumes that a persistent CSF leak through the dura mater results in prolonged loss of a larger volume of CSF and, therefore, accounts for a prolonged reduction in CSF volume.

An interesting possibility is the release of endorphins as a result of LP. There is some evidence for an increase in endogenous morphines in the CSF after acupuncture for recurrent pain.[15,16] The analgesic effect of the endorphins is nevertheless of short duration[17] and does not explain the prolonged relief of headache found in our patients.

In conclusion, this investigation has verified the clinical impression that LP does alleviate some of the clinical manifestations of viral meningitis. The exact mechanism or mechanisms mediating this change have not been elucidated. It is possible that a slight ICP increase occurs in viral meningitis that activates pain-sensitive receptors in the meninges. The small ICP fall due to the CSF withdrawal, possibly increased by a subsequent CSF dural leak, may be sufficient to decrease this pain stimulus. The decrease in headache could also result in the improvements of the less-specific clinical phenomena that were found. This theory could be investigated by CSF pressure measurements before and after LP; however, technically this is difficult to accomplish because of the noncooperation of the average pediatric patient.

Lumbar puncture is not indicated for the relief of symptoms in viral meningitis, even though it is frequently used this way. It is useful and valuable for diagnostic purposes only.

References

1. Wilton NCT, Globerson JH, DeRosayro AM. Epidural blood patch for postdural puncture headache: it's never too late. *Anesth Analg.* 1986;65:895-896.
2. Rosenberg PH, Heavner GE. In vitro study of the effect of epidural blood patch on leakage through a dural puncture. *Anesth Analg.* 1985;64:501-504.
3. Jarvis AP, Greenawalt JW, Fagraeus L. Intravenous caffein for postdural puncture headache. *Anesth Analg.* 1986;65:316-317.
4. Bolder PM. Post lumbar puncture headache in pediatric oncology patients. *Anesthesiology.* 1986;65:696-698.
5. McCarthy PL, Sharpe MR, Spiesel SZ, et al. Observation scales to identify serious illness in febrile children. *Pediatrics.* 1982;70:802-809.
6. Goitein KJ, Amit Y, Mussaffi H. Intracranial pressure in central nervous system infections and cerebral ischemia of infancy. *Arch Dis Child.* 1983;58:184-186.
7. Kaplan SL, Fishman MA. Supportive therapy for bacterial meningitis. *Pediatr Infect Dis J.* 1987;6:670-677.
8. McComb JG. Recent research into the nature of cerebrospinal fluid formation and absorption. *J Neurosurg.* 1983;59:369-383.
9. Cutler RWP, Page L, Galicich J, Watters GV. Formation and absorption of cerebrospinal fluid in man. *Brain.* 1968;91:707-720.
10. Takizawa H, Gabra-Sanders T, Miller JD. Variations in pressure-volume index and CSF outflow resistance at different lcoations in the feline craniospinal axis. *J Neurosurg.* 1986;64:298-303.
11. Shapiro K, Fried A. Pressure-volume relationships in shunt dependent childhood hydrocephalus. *J Neurosurg.* 1986;64:390-396.
12. Shapiro K, Marmarou A, Shulman K. Characterisation of clinical CSF dynamics and neural axis compliance using the pressure-volume index: 1. the normal pressure-volume index. *Ann Neurol.* 1980;7:508-514.
13. Lorenzo AV, Page LK, Watters GV. Relationship between cerebrospinal fluid formation, absorption and pressure in human hydrocephalus. *Brain.* 1970;93:679-692.
14. Welch K. The principles of physiology of the cerebrospinal fluid in relation to hydrocephalus including normal pressure hydrocephalus. *Adv Neurol.* 1975;13:247-332.
15. Clement Jones V, Tomlin S, Rees LH, McLoughlin L, Besser GM, Wen HL. Increased β-endorphin but not metenkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. *Lancet.* 1980;2:946-948.
16. Sjoland B, Eriksson M. Electro-acupuncture and endogenous morphins. *Lancet.* 1976;2:1085.
17. Graf L, Szekely JI, Ronai AZ, Dunai-Kovacs Z, Bajusz S: Comparative study on analgesic effect of met-enkephalin and relative lipotropin fragments. *Nature.* 1976;263:240-241.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Histologic Manifestations of Perinatal Genital Mycoplasmal Infection

Elio Madan, MD; Michael P. Meyers, MS; Antonio J. Amortegui, MD (*Arch Pathol Lab Med.* 1989;113:465-469)

Vitamin K Absorption Capacity and Its Association With Vitamin K Deficiency

Takeshi Shinzawa, MD; Tetsuo Mura, MD; Mikio Tsunei, MD; Kazou Shiraki, MD

• We measured plasma vitamin K concentrations in 194 5-day-old infants three hours after administration of a 4-mg dose of vitamin K (menaquinone-4, Kaytwo syrup, Eisai Co Ltd, Tokyo, Japan). We investigated association with other factors contributing to vitamin K deficiency. These plasma vitamin K concentrations varied greatly among the neonates from values below the limit of detection (2 ng/mL) to more than 1000 ng/mL. The vitamin K concentration was associated with nutritive vitamin K deficiency represented by plasma protein induced by vitamin K absence or antagonist-II (PIVKA-II) values. The wide variation in vitamin K absorption is considered to be one of the major causative factors in infantile vitamin K deficiency.

(*AJDC* 1989;143:686-689)

The prognosis of "late hemorrhagic disease of the newborn (HDN)" is poor, and prophylactic administration of vitamin K has been recommended. A nationwide survey in Japan revealed that 82.7% of infants with late HDN had intracranial hemorrhage and that "idiopathic" vitamin K deficiency accounts for about 88% of all patients.[1] To clarify the cause of idiopathic infantile vitamin K deficiency, vitamin K absorption via the intestine should be studied, as well as vitamin K supply and vitamin K utilization. There are only a few reports, such as the studies by McNinch et al[2] and Sann et al,[3] on the role of orally administered vitamin K in the neonatal period, especially in patients with this disease. We evaluated the absorption of orally administered menaquinone-4 (MK-4) in 194 infants and studied its association with other factors contributing to vitamin K deficiency.

Accepted for publication Oct 19, 1988.

From the Department of Pediatrics (Drs Shinzawa, Tsunei, and Shiraki) and the Division of Chemistry (Dr Mura), Institute of Steroid Research, Tottori University School of Medicine, Yonago, Japan.

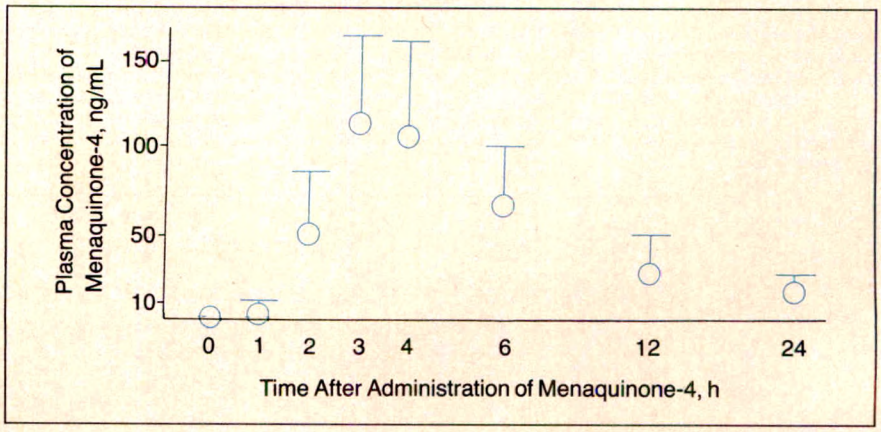
Reprint requests to Department of Pediatrics, Tottori University School of Medicine, 36-1 Nishimachi, Yonago 683, Japan (Dr Shinzawa).

PATIENTS AND METHODS

A 1/10 dilution of 2 mL of a syrup containing 4 mg of MK-4 (menaquinone-4, Kaytwo syrup, Eisai Co Ltd, Tokyo, Japan) was administered to 5-day-old infants who were born at full-term at the Obstetric Department of Tottori University Hospital, Yonago, Japan, from October 1986 through September 1987. None of them vomited the syrup, and blood sampling was done after three hours. During these three hours, milk was not given to the infants. We examined plasma concentrations of vitamin K, protein induced by vitamin K absence or antagonist-II (PIVKA-II), and total bile acid. We remeasured PIVKA-II, total bile acid, and Normotest values in these infants when they were 3 weeks of age. The Normotest, for which we used a commercially available kit (Eisai Co Ltd), measures the total activity of vitamin K–dependent coagulation factors II, VII, and X, and requires only 25 μL of whole blood. Only neonates from whom blood was collected during fasting before feeding were included in this study, and those who developed diarrhea or fever, those who received antibiotics, and high-risk neonates with underlying disease were excluded. Thus, of 278 births during this period, 194 infant measurements were analyzed. These infants were all breast-fed (and were given an additional glucose solution) five days after birth, and 98 were breast-fed, 83 were mixed-fed, and 13 were bottle-fed three weeks after birth. In addition, MK-4 concentrations at 1, 2, 3, 4, 6, 12, and 24 hours after the administrations of the syrup were determined in six infants at 5 days of age. Informed consent was obtained from all mothers. Plasma and serum were kept at −80°C until analyzed.

Plasma MK-4 concentrations were measured by the method of Shirahata and Kayashima.[4] Vitamin K_1 (phytonadione) or MK-3 (50 ng) as an international standard was added to plasma (0.5 mL), and then distilled water (2 mL) and isopropyl alcohol (4 mL) were added and the sample was mixed thoroughly. After *n*-hexane (10 mL) was added, the mixture was shaken vigorously for five minutes and centrifuged at 3000 rpm for five minutes. The supernatant was obtained, evaporated with N_2 gas, and redissolved in isopropyl alcohol (100 μL). A 20-μL aliquot was subjected to high-performance liquid chromatography (separation column: Finepak Sil C18 Japan Spectroscopic Co Ltd, Tokyo, Japan; liquid: 95% ethanol, 0.5 mL/min; reagent: 0.01% $NaBH_4$; ethanol solution; fluorometric determination: excitation—335 nm, emission—450 nm), and the area of the chromatogram was compared with a vitamin K standard to calculate plasma vitamin K concentrations. Plasma PIVKA-II was measured using an enzyme immunoassay kit (E-1023, Eisai Co Ltd) developed by Motohara et al[5] and the values were expressed in

Fig 1.—Changes in plasma menaquinone-4 concentration after administration of 4 mg to six infants at 5 days of age. Circles and bars represent means ± SDs.



arbitrary units (AU) per milliliter. One AU corresponded to 1 μg of purified prothrombin. Total bile acid was determined by enzyme fluoroassay (neosterognost-3α, Daiichi Kagaku, Tokyo, Japan).

Normotest reflects the total activity of vitamin K–dependent coagulant factors II, VII, and X. It is a simple and convenient assay of the vitamin K–dependent coagulant activity for an infant because it requires only 25 μL of whold blood. We administered additional oral (or intravenous) vitamin K if its value was lower than 40% at three weeks after birth.

RESULTS

Plasma Vitamin K Concentrations

Using the standard of vitamin K series (phytonadione and MK-3 to MK-9) revealed that the limit of vitamin K detection by this method was 0.2 ng (plasma concentration, 2 ng/mL), and each component was clearly separated. The coefficient of variation for ten measurements in the same sample was 5.9%.

Changes in Plasma Vitamin K Concentration After Syrup Administration

Changes in the plasma vitamin K concentration were evaluated after a single administration of 4 mg of MK-4 to six infants (Fig 1). Before administration, the chromatogram showed no peak according with vitamin K series (phytonadione and MK-3 to MK-9) in all six infants. The plasma MK-4 concentration was still below the level of sensitivity in three infants one hour later. The MK-4 level reached a peak concentration in three to four hours and decreased gradually in all infants. The plasma concentration three hours after administration was considered to represent the capacity for vitamin K absorption. No infant showed the peak of vitamin K series except for MK-4.

Vitamin K Absorption Capacity

Since 4 mg of MK-4 was administered to all infants, the plasma MK-4 concentrations were corrected for weight and expressed in terms of the following index: absorption index = MK-4 concentration × weight (in kilograms)/administered MK-4 (4 mg). This index theoretically corresponds to the plasma MK-4 concentration after administration at a dose of 1 mg/kg. The distribution of values of this index plotted on a semilogarithmic graph (Fig 2) revealed marked individual differences in vitamin K absorption among these neonates without underlying disease who were born by normal full-term delivery. The index varied widely from that below the detection limit in seven neonates (3.6%) to the highest value of 820 with the mean (± SD) being 125.0 ± 137.5. Figure 3 shows the chromatogram of vitamin K analyses of two infants. The chromatogram of patient 1 showed high peak of MK-4, but that of patient 2 showed no peak of MK-4.

Vitamin K Absorption Capacity and PIVKA-II at Five Days After Birth

The vitamin K absorption index was bilogarithmically plotted against PIVKA-II at five days after birth to evaluate their possible correlation (Fig

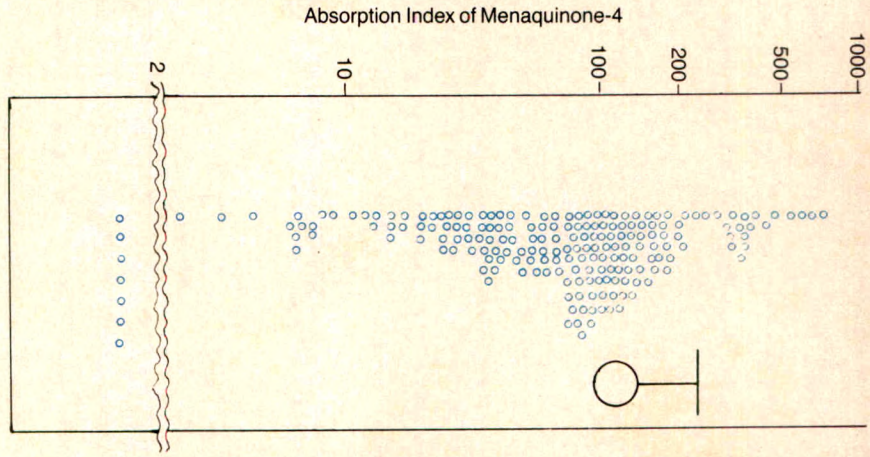


Fig 2.—Distribution of values of menaquinone-4 absorption index in 194 cases of 5-day-old infants. Circle and bar represent mean ± SD.

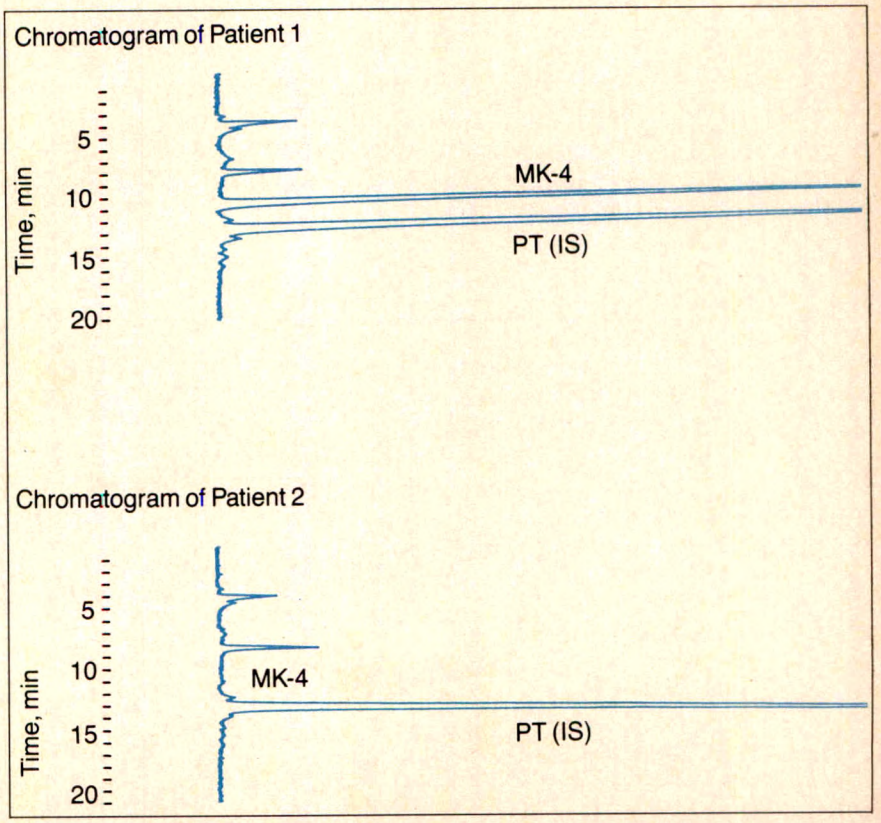


Fig 3.—Chromatogram of vitamin K analyses in two patients. Plasma concentration of menaquinone-4 (MK-4) after administration at three hours was high in patient 1. In patient 2, chromatogram showed no peak according with MK-4. PT indicates phytonadione; IS, internal standard.

4). For convenience, the detection limit (0.063 AU/mL for PIVKA-II and 2 ng/mL for MK-4) was used at calculation instead of values below the detection limit. A significant negative correlation was observed ($r = -.319$, $P < .01$) between these factors, suggesting a strong association between the individual difference in vitamin K absorption and vitamin K deficiency.

Vitamin K Absorption Capacity and Total Serum Bile Acid

The total serum bile acid level five days after birth was 20.1 ± 10.2 μmol/L. The MK-4 absorption index was semilogarithmically plotted against the total serum bile acid level to evaluate their possible correlation (Fig 5). Vitamin K absorption was poor in neonates with markedly high serum total bile acid levels. However, some neonates with extremely low total bile acid levels also showed values below the analysis limit, demonstrating no direct correlation between these factors.

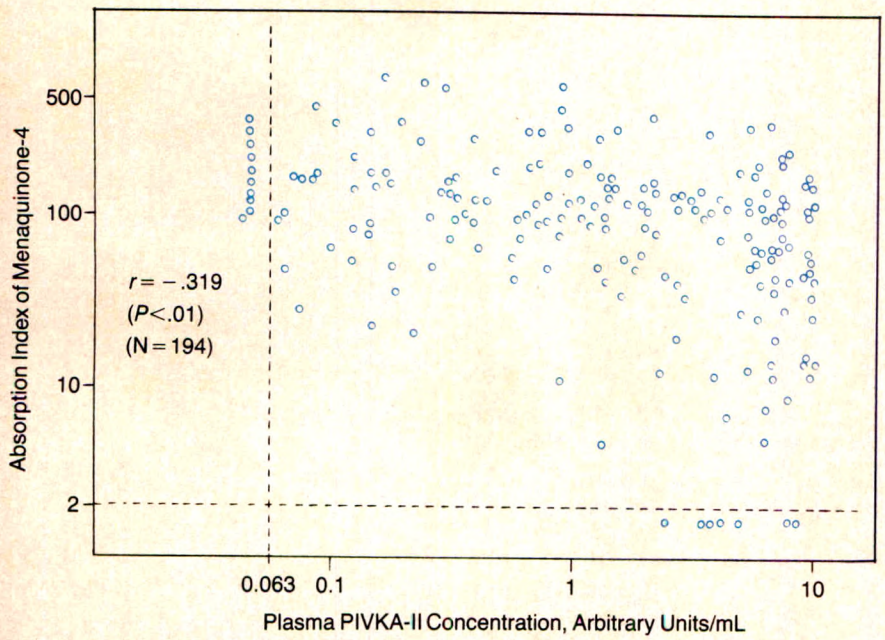


Fig 4.—Absorption index of menaquinone-4 and protein induced by vitamin K absence or antagonist-II (PIVKA-II) at five days after birth.

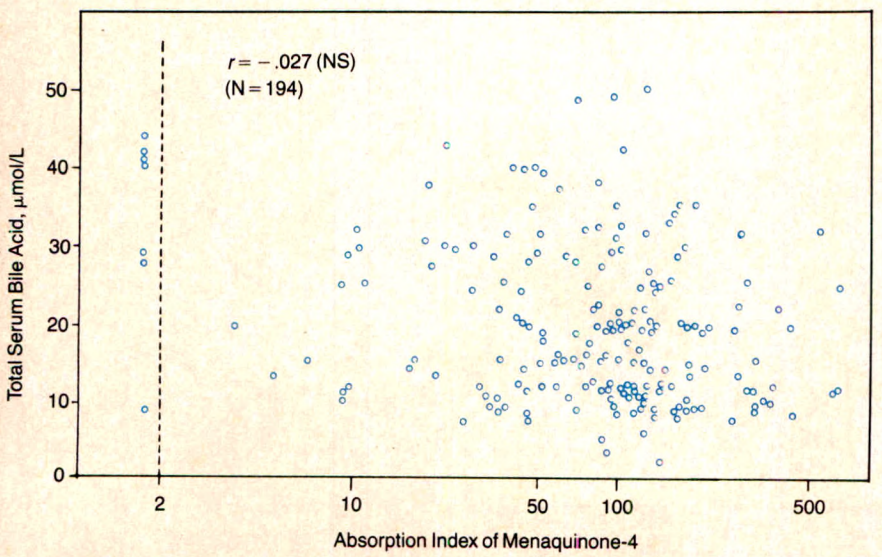


Fig 5.—Absorption index of menaquinone-4 and total serum bile acid value at five days after birth. NS indicates not significant.

Profiles of Infants With MK-4 Concentration Below the Detection Limit Three Hours After Administration

To evaluate the association between failure to absorb vitamin K at 5 days of age and the presence of vitamin K deficiency at 3 weeks of age, we examined profiles of infants with MK-4 concentration below the detection limit three hours after administration (Table). As background information, we previously reported that PIVKA-II was positive during the early neonatal period in most mature 5-day-old infants not treated with vitamin K; its value was 0.13 AU/mL or more in 91.8%, of whom 31.7% showed values of 4 AU/mL or more. However, in most of the neonates treated with vitamin K (4 mg) five days after birth, PIVKA-II became negative three weeks after birth; it was positive only in 14 (7.2%) of the treated infants but not strongly positive in any of them.[6] All of the neonates showing MK-4 concentrations below the detection limit (except for one infant) were strongly positive for PIVKA-II at 5 days of age and were included in the positive 7.2% neonates three weeks after birth. These results suggest that poor vitamin K absorption in the early neonatal period is associated with the presence of vitamin K deficiency in the late neonatal period.

Total serum bile acid level three weeks after birth was 29.9 ± 17.1 μmol/L, which was elevated from that five days after birth. We did not demonstrate direct correlation between the index of MK-4 absorption and total serum bile acid concentration; patients 2, 3, and 6 showed significantly higher total bile acid levels (more than mean ± SD) both at five days and at three weeks after birth. In these patients, poor vitamin K absorption was probably due to poor bile acid secretion in the intestine.

Normotest is widely used for the screening of vitamin K deficiency in Japan. If its value was lower than 40% at three weeks after birth, we administered additional vitamin K to the pa-

Profiles of Seven Infants Whose Plasma Menaquinone-4 Concentrations Were Below Limit of Detection After Administration of 4 mg of Drug*

Case/ Birth Weight, g/ Sex	Total Bile Acid, μmol/L		PIVKA-II, AUs/mL		Feeding	Normotest, % at 3 wk After Birth
	5 d After Birth	3 wk After Birth	5 d After Birth	3 wk After Birth		
1/4240/F	27.2	38.9	4.8	0.40	Breast	40
2/3094/F	44.4	105.6	6.9	0.20	Breast	46
3/2856/F	32.0	86.4	5.9	0.15	Breast	60
4/2816/F	41.4	25.8	9.0	0.03	Bottle	100
5/3000/M	8.6	46.2	3.6	0.15	Breast	55
6/3220/M	40.2	79.6	5.5	0.17	Breast	60
7/2608/F	28.6	40.4	9.2	0.46	Mixed	80

*PIVKA-II indicates protein induced by vitamin K or antagonist-II; AUs, arbitrary units.

tient. In our 194 infants, the mean (±SD) Normotest value was 78% ± 17% at three weeks after birth. In the seven infants showing MK-4 concentration below the detection limit, additional vitamin K was administered to only one infant. These results showed that the presence of a small dose of PIVKA-II was not always associated with low vitamin K–dependent coagulant activity.

COMMENT

To clarify the cause of idiopathic infantile vitamin K deficiency, vitamin K supply determined by vitamin K concentrations in breast milk and milk dose given to the infant, absorption of orally administered vitamin K, and utilization of vitamin K in the liver should be studied. Miyaji et al[7] reported that vitamin K concentrations in breast milk were lower in mothers of infants with this disease than in controls. However, the vitamin K concentrations in breast milk in vitamin K deficiency considerably overlapped those of the control mothers. The difference of vitamin K concentrations in breast milk between the mothers of the patients and those of controls was not wide, no more than half. Therefore, low vitamin K concentrations in breast milk may not be the only factor causing vitamin K deficiency in infancy. Motohara et al[8] reported a significant correlation between PIVKA-II values during the early neonatal period and milk dose given to the infants. Although similar results were obtained in our previous studies,[6] the correlation between PIVKA-II and the dose fed was less important during the late neonatal period than during the early neonatal period. In addition, no correlation was observed between the PIVKA-II value during the early neonatal period and that measured during the late neonatal period in the same infant. These results suggested that other additional factors were associated with hemorrhagic disease occurring during the late neonatal period. There have been some studies of vitamin K concentrations after oral administration of vitamin K,[2,3,9] but there are, to our knowledge, no reports that evaluate the relationship between neonatal vitamin K absorption capacity and vitamin K deficiency in a large number of subjects. Because this brand of MK-4 syrup has been widely used for vitamin K prophylaxis in Japan, we used it in the present study. However, we hope to study oral vitamin K_1 absorption in future studies.

In our study, even though the subjects were normal 5-day-old infants born at full-term, MK-4 absorption varied widely and was strongly associated with nuturitive vitamin K deficiency represented by PIVKA-II values. These results suggest that an individual difference in vitamin K absorption via the intestine together with its supply plays an important role in the development of this disease.

Our previous analysis of serum bile acid revealed a group showing a marked cholestatic pattern in cases of idiopathic infantile vitamin K deficiency.[10] In our study, no close correlation was observed between one point serum bile acid values and MK-4 absorption. Although the energy system reported by Hollander[11] is involved in lipid-soluble vitamin absorption, some neonate with plasma MK-4 concentration under the detection limit showed high bile acid levels in both an early neonatal period and in the late neonatal period. Bile acid secretion could not be evaluated by one point serum bile acid values, but from these results, insufficiency of bile acid secretion into the intestine might be related to vitamin K absorption via the intestine.

Our results suggest an important association of poor vitamin K absorption to developing vitamin K deficiency.

The authors thank Eisai Co Ltd, who generously supplied the PIVKA-II enzyme immunoassay kits.

References

1. Hanawa Y, Maki M, Murata B, et al: The second nation-wide survey in Japan of vitamin K deficiency in infancy. *Eur J Pediatr* 1988;147: 472-477.

2. McNinch AW, Upton C, Samuels M, et al: Plasma concentrations after oral or intramuscular vitamin K_1 in neonates. *Arch Dis Child* 1985; 60:814-818.

3. Sann L, Leclercq M, Guillaumout M, et al: Serum vitamin K_1 concentrations after oral administration of vitamin K_1 in low birth weight infants. *J Pediatr* 1985;107:608-611.

4. Shirahata S, Kayashima N: Analytical method of vitamin K (in Japanese). *Med Way* 1985;2:71-74.

5. Motohara K, Kuroki Y, Kan H, et al: Detection of vitamin K deficiency by use of an enzxyme-linked immunosorbent assay for circulating abnormal prothrombin. *Pediatr Res* 1985;19:354-357.

6. Shinzawa T, Tsunei M, Shiraki K: The values of PIVKA-II in the early neonatal period (in Japanese). Read before the 23rd Congress of Japan Society of Neonatology, Matsue, Japan, 1987.

7. Miyaji Y, Mori N, Meguro T, et al: Vitamin K in breast milk (in Japanese). *Perinat Med* 1982;12:1107-1112.

8. Motohara K, Matsukane I, Endou F, et al: Role of milk intake in early neonatal vitamin K deficiency (in Japanese). *Acta Pediatr Jpn* 1987;91:1435-1441.

9. Komazawa M: Intestine and vitamin K: Vitamin K absorption (in Japanese). *Jpn J Pediatr Med* 1984;16:867-870.

10. Shinzawa T, Yamada K, Shiraki K, et al: Bile acid metabolism in infantile vitamin K deficiency (in Japanese). *Acta Pediatr Jpn* 1987;91:1219-1223.

11. Hollander D: Intestinal absorption of vitamin A, D, E and K. *J Lab Clin Med* 1981;97:449-452.

Evaluation of a Camp Program for Siblings of Children With Cancer

Olle Jane Z. Sahler, MD, Paul J. Carpenter, PhD

• **In recent years, specialized camping programs for chronically ill children, members of their family, or both have proliferated. Although these programs are popular, little systematic evaluation of risk-benefit has been undertaken. In a naturalistic study we evaluated the effect of a 5-day residential camping program to determine the effect of the program on the level of medical knowledge, on the perceptions of how the cancer experience affected the individual, and on the participant's mood state. Analyses of questionnaire data from 90 campers before and after their participation in the program revealed that desirable changes occurred in each of these areas and were sustained for at least 3 months after the program. Siblings reported by parents to have behavioral problems with onset since the diagnosis of the cancer seemed to benefit particularly from this type of program. No substantial negative effects were found regardless of the camper age, adaptational status, or previous camp experience.**

(*AJDC*. 1989;143:690-696)

Specialized camping programs for chronically ill children, members of their family, or both have proliferated in recent years. Although the popularity of such programs has been high, little systematic evaluation of risk-benefit has been undertaken. This article focuses on a 5-day residential camping program for siblings of children with cancer that was designed to (1) provide a recreational experience, (2) enhance knowledge about cancer, and (3) facilitate meeting other siblings experiencing a similar family crisis. (Camp B&ST [*B*rothers & *S*isters *T*ogether] was developed through the mutual efforts of Camp Good Days and Special Times Inc, a community-based, nonprofit organization that supports programs for pediatric patients with cancer and their families, and the Division of Pediatric Hematology/Oncology at the University of Rochester [NY] Medical Center.)

A naturalistic study was undertaken to evaluate the effect of the program (1) on the level of medical knowledge, (2) on the perceptions of how the cancer experience affected the individual, and (3) on the participant's mood state. Analyses of questionnaire data from 90 campers before and after their camp experience revealed that desirable changes occurred in each of these areas and were sustained for at least the 3-month follow-up period. Siblings reported by parents to have behavioral problems with onset since the diagnosis of the cancer seemed to benefit particularly from the program. No significant negative effects were found regardless of camper age, adaptational status, or previous camp experience.

The informal recreation-centered atmosphere of summer camp provides an attractive setting in which to introduce individuals with a chronic disease or handicapping condition to one another and to provide instruction about the disease and ways to cope with it. Another appealing aspect of such programs is that the campers are naturally placed into situations that require independent and autonomous behavior fostered by the peer-group interactions rather than by reliance on parental judgment or adult supervision. The many anecdotal accounts[1-4] of the positive effects of such experiences on sick or handicapped children are being validated by systematic studies.[5,6]

Although camping programs have been developed for a variety of patient populations, few have been developed for other family members. This article describes a camping program designed specifically for siblings of children with cancer and presents the findings of a naturalistic evaluation of the efficacy of the camp program as it was designed and implemented by a community-based special interest support group.

DESCRIPTION OF THE CAMP PROGRAM

In 1982 a camp was initiated in the upstate New York area for school-age children and adolescents who, although healthy themselves, are the siblings of children with cancer.[7]

The goals of the camp are as follows: (1) to provide a recreational experience, (2) to enhance campers' knowledge about cancer, and (3) to provide an opportunity to meet other siblings experiencing a similar family crisis. Thus, although recreational activities comprise the major component of the camp, medical information is also disseminated and peer-group support is fostered through formal and informal group activities.

Siblings between the ages of 6 and 17 years who have a brother or sister treated at any of the upstate New York pediatric oncology centers are invited to attend. Enrollment has grown from 33 in 1982 to a maximum of 110 in 1986. Reenrollment exceeds 50%.

The camp is a 5-day residential program. The first day of camp is reserved for orientation and recreational activities. On the second day, each camper attends an hour-long, small group, medical information session led by a pediatric oncologist and an oncology nurse specialist. To provide instruction at an appropriate cognitive level, camper assignment to the workshops is deter-

Accepted for publication December 31, 1988.

From the Department of Pediatrics (Dr Sahler) and the Department of Pediatrics and the Cancer Center (Dr Carpenter), University of Rochester (NY) Medical Center.

Presented in part at the annual meeting of the Ambulatory Pediatric Association, April 30, 1987, Anaheim, Calif.

Reprint requests to Box 690, Department of Pediatrics, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Sahler).

mined by age (6 to 11 years or 12 to 17 years). The sessions are highly experiential and include opportunities for the campers to handle medical equipment. Various medical terms, procedures, and therapies are defined and their function in the management of childhood cancer is explained.

Psychosocial support sessions are usually conducted on the third day of camp. Groups are composed of campers of similar ages who are further divided into groups of campers whose brother or sister is alive and campers who are bereaved. Sessions are preceded by skits depicting common themes in families with childhood cancer (eg, parents not having time to attend a school play with the healthy sibling). Outlines for these skits, which are staged by a local improvisational theater group, are developed in consultation with camp personnel, some of whom are themselves young adult siblings of pediatric patients with cancer. Following each vignette, "in character" discussions to clarify feelings occur between the actors and the audience. After the presentations, the siblings meet in groups with a psychologist, social worker, or behavioral pediatrician to discuss the issues and concerns raised by the skits or other similar issues of interest. A lay camp counselor also is included in each group as a resource person to provide support to individual campers as needed either during or after the session. Although attendance is voluntary, about 95% of campers choose to participate.

EVALUATION OF THE CAMPING PROGRAM

Over the course of two summers an evaluation of the experience of attending camp was undertaken. Consistent with the goals of the camp, our overall hypotheses were that attendance would (1) increase campers' knowledge regarding medical therapies and procedures, and (2) positively modify campers' perceptions of how having someone with cancer in the family has affected them and their lives. In evaluating these hypotheses, we examined the potential effects of three independent sibling variables: (1) age, (2) presence or absence of problems adjusting to the cancer experience as reported by their parents, and (3) previous camp experience. The rationale for examining these specific variables is based on our previous findings that age substantially affects the level of cognitive understanding of cancer and that the presence of adaptational problems influences certain perceptions of how the pediatric cancer experience has affected self and relationships with others.[8] In addition, because about half of the campers had been to the camp before, we examined the effect of previous camp experience on current knowledge and perceptions of cancer.

The intent of this investigation was to systematically assess the influence of the camping experience as it was designed and naturally occurred. Thus, there was no attempt to control for confounding variables or to assign siblings to intervention groups. Participation in the camp program is voluntary. All siblings of children treated at the participating institutions are informed of the availability of the camp and scholarship aid is provided to families in need of assistance. Preceding and during the summers included in this study, no child who wished to enroll had ever been denied entry to camp.

METHODS

Subjects

Subjects consisted of all siblings registering for the camp during the first summer of evaluation and all new campers registering the next summer.

Design

Precamp and postcamp analyses, within subjects design was used to evaluate the specific hypotheses outlined above. Data were collected during the month and 3 months after camp ended.

Assessment Questionnaire

Assessment questionnaires were developed for campers and their parents.[9] Items were written in consultation with oncology specialists and several siblings and were chosen for inclusion on the apparent relevance to the specific study population.

Sibling Questionnaire.—As shown in Table 1, the sibling questionnaire assessed two primary content domains: (1) *knowledge* about cancer and its treatment; and (2) *perceptions and affective responses* about the influence of the cancer experience as it relates to self, family relationships, and nonfamily relationships.

Questions assessing medical information focused on eight common cancer-related procedures or therapies. Knowledge was mea-

Table 1.—Domains and Items Comprising the Sibling Perception Questionnaire

Medical Knowledge
Identification items
A blood count or "counts" is
A bone marrow test is
A spinal tap or "spinal" is
An IV is
Chemotherapy or "chemo" is
Radiation is
A Broviac or Hickman catheter is
An operation or surgery is
Instrumental understanding items
Some kids with cancer get "counts" because
Perceptions of Disease Influence
Factor 1—interpersonal
I wish my parents would spend less time with my brother/sister (B/S)
I wish my parents would spend more time with me
People are more interested in my B/S than me
People don't care how I feel
My parents ignore me
I have too much to do in the house once my B/S got sick
I don't want to bother my parents with my worries
I wish I knew someone who understands how I feel
We don't do much as a family since my B/S got sick
Factor 2—intrapersonal
I feel sad about my B/S cancer
I wish there was something I could do about my B/S cancer
I think about my B/S cancer
I wonder why my B/S got sick
I feel mad about my B/S cancer
I understand why my parents have to spend time with my B/S
I can forget that my B/S has cancer
Factor 3—communication
I can talk to my parents about my B/S cancer
I can talk to other adults about my B/S cancer
I can talk to my parents about my school work
I can talk to my friends about my B/S cancer
Factor 4—fear of disease
I worry that I can catch cancer from my B/S
I am afraid of my B/S cancer
My friends worry that they can catch cancer from my B/S
Mood
Positive
Happy
Energetic
Active
Friendly
Loving
Cheerful
Relaxed
Contented
Negative
Nervous
Sad
Angry
Miserable
Afraid
Irritable

Table 2.—Sample Characteristics (N=90)

Campers (Siblings)	
Age, y (range)	11.2 (6-17)
School grade (range)	5th (1-11)
Sex, %	
M	51
F	49
Adaptational problems (parent-reported) since diagnosis, %	
Yes	55
No	45
Previous camp attendance, %	
Yes	46
No	54
Child With Cancer	
Sex, %	
M	54
F	46
Age at diagnosis, y (range)	7.6 (1-17)
Time since diagnosis, y (range)	4.0 (0.3-13)
Type of cancer, %	
Leukemia (all types)	50
Solid tumor	20
Lymphoma	15
Brain tumor	15
Family	
Marital status, %	
Intact	86
Divorced/ separated/ single	14
Parental Education, %	
Completed high school	95
Less than high school	50

sured in two areas: (1) *identification* (the ability to define a procedure or therapy), and (2) *instrumental understanding* (the ability to describe why a child with cancer might receive a particular procedure or therapy). Questions were presented in a sentence completion–type format and were scored by one of two independent raters according to an objective rating schema developed by us. Interrater reliability was 85%.

Siblings' perceptions and affective responses were assessed specifically and globally. Responses specific to the influence of cancer were assessed using 27 items that addressed issues relevant to siblings as suggested by the literature[10,11] and clinical experience (see Table 1). Each item was rated using Likert-type scales (never/a little/sometimes/a lot/always).

Factor analysis revealed that 23 items loaded on four primary factors. The items loading on factor 1 (percentage of variation = 48.6) relate primarily to interpersonal interactions and relationships and was labeled "interpersonal." The items comprising factor 2 (percentage of variation = 31.3) focus on how the chronic illness affects the individual and was labeled "intrapersonal." The items in factor 3 (percentage of variation = 11.1) all contain the words "talk... about" and was labeled "communication." The three items comprising factor 4 (percentage of variation = 9.0) relate to "catching cancer" and was labeled "fear of disease." The internal consistency reliability of the factors ranged from 0.65 to 0.86.

Global responses to the influence of cancer were assessed using eight positive and six negative mood states as a reflection of current general well-being. The particular mood states were chosen because of their face validity and sensitivity in detecting distress.[12] Siblings responded to the mood state items according to the same five-point Likert scale discussed previously.

Parent Questionnaire.—The parent questionnaire also was designed to assess perception of specific and global responses of the siblings to the cancer experience. The open-ended question, "What problems, at home or school, has your child had since his/her brother/sister was diagnosed with cancer?" was used to identify specific behavioral responses. Answers to this question were not corroborated by data from any independent sources as parents have been shown to be reliable and valid observers and reporters of their children's development, behavior, and psychosocial adaptation.[13] Parental perceptions of their child's global responses were assessed by having them rate their child's current mood state.

Procedure

The questionnaires were completed by camp participants and their parents as part of the routine registration procedure. A consent form, approved by the Committee on Investigations Involving Human Subjects, accompanied the materials and was signed by the camper and his or her parent(s). In families where more than one sibling was registered for camp, a separate set of questionnaires was completed by and for each child. Instructions for completing the questionnaire were included with the research forms. Because some of the younger campers might have had difficulty completing the questionnaire, parents were instructed to help their child if necessary but to complete any open-ended questions in the child's words. A self-addressed, stamped envelope was provided for questionnaire return.

Follow-up questionnaires were mailed to campers and parents 3 months after camp ended. Instructions for completing the questionnaires, which were identical to those sent during the camp registration period, were enclosed. Return postage was prepaid.

Statistical Analysis of the Data

Paired *t*-Tests (one tailed) were used to analyze siblings' responses to the questionnaire before and after attending camp. Because predictions regarding all results were made a priori, the use of multiple *t*-tests are statistically appropriate and provide adequate protection against type I error. Differences at an α level of $P \leq .09$ are reported to include information about trend effects.

RESULTS

Of the 150 eligible campers, 141 (94%) of the siblings and their parents completed the precamp questionnaire; 99 (71%) of the study participants completed the postcamp questionnaires; and 90 (65%) completed precamp and postcamp questionnaires. This group of 90 subjects constitutes the sample for this study

As shown in Table 2, the average camper was 11.2 years old (range, 6 to 17 years) and in the fifth grade (range, grade 1 to 11). The percentages of males and females were equal. Fifty-five percent (49/90) of the campers had adaptational difficulties as reported by their parents; these included changes in sleeping or eating patterns, behavioral difficulties at home, attitudinal or academic difficulties at school, and psychosomatic complaints. Fifty-four percent (48/90) were first-time campers.

With respect to the siblings' sick brother or sister, 54% (48/90) were male and were, on the average, 7.6 years of age when cancer was diagnosed. Fifty percent (45/90) were diagnosed with leukemia, 20% (18/90) with solid tumors, 15% (13/90) with lymphomas, and 15% (13/90) with brain tumors. The average time since diagnosis was 4 years (range, 4 months to 13 years). Eighty-six percent (77/90) of the campers were from intact families. Ninety-five percent (85/90) of the parents had completed high school and 50% (45/90) had received education beyond high school.

Analysis of Responders vs Nonresponders

One-way ANOVAs and the χ^2 method were used to compare those campers who did and did not return both sets of questionnaires. No between-group differences for current age, sex, or presence of adaptational problems as reported by parents previous camp experience

were found. The only variable that significantly differentiated the two groups was time since diagnosis. Those campers who completed only the precamp questionnaire were significantly further away from the time of diagnosis than those who completed both (4.8 vs 3.4 years; $P<.05$). In addition, analysis of the items outlined in Table 1 revealed that only five (6%) emerged as significantly different for the two groups on the precamp questionnaire, a difference that could be expected by chance alone. Thus, no systematic bias seemed to distinguish prestudy and poststudy participants from nonparticipants.

Analysis of Precamp and Postcamp Assessments

Total Sample.—The overall effect of attending camp on siblings' fund of medical knowledge, perceptions of disease influence, and mood state was determined by calculating a summary score for each subgroup or factor within each domain. Table 3 presents the before and after findings for the total sample (N = 90).

As can be seen, significant precamp and postcamp changes occurred in the campers' level of medical knowledge in the areas of identification and instrumental understanding. Precamp and postcamp effects were also noted for the intrapersonal and fear of disease factors and for positive and negative moods as reported by campers and by their parents. All differences with a P value <.09 were in the desired direction.

Effects of Age, Perceived Adaptational Status, and Previous Camp Experience.—*Age: Medical Knowledge.*—Table 4 presents the comparison of younger (<12 years) and older (≥12 years) campers at the precamp and postcamp assessments and the precamp and postcamp differences. Analysis of the precamp and postcamp assessments reveals that the younger campers' scores were significantly lower than the older campers' scores for identification ($P<.01$) and instrumental understanding ($P<.01$).

When time since diagnosis was controlled for to ascertain potential effects of ongoing instruction about or familiarity with the disease that might result from repeated contact with, for example, health care givers, no correlation

Table 3.—Effects of Attending Camp B&ST on Siblings' Medical Knowledge, Perceptions of Disease Influence, and Mood for the Total Sample (N = 90)

Domain	No. of Items Comprising Each Domain	% of Items With Significant Precamp and Postcamp Change*	Precamp and Postcamp Analyses (Paired *t* Tests; One-Tailed *P*)
Medical knowledge			
Identification	8	25	<.02
Instrumental	8	25	<.01
Perceptions			
Interpersonal	9	17	NS
Intrapersonal	7	100	<.00
Communication	4	25	NS
Fear of disease	3	33	<.09
Moods			
Camper self-report			
Positive	8	38	<.02
Negative	6	67	<.00
Parent report			
Positive	8	25	<.05
Negative	6	67	<.00

*All significant changes are in the desired direction.

Table 4.—Effect of Age on Outcome Measures*

Outcome Variable	Desired Direction of Change	Precamp, Mean (SD)			Postcamp, Mean (SD)			Precamp vs Postcamp Results, *P*	
		Younger	Older	*P*	Younger	Older	*P*	Younger	Older
Medical knowledge									
Identification	+	9.43 (4.46)	15.11 (6.20)	<.01	10.46 (5.81)	16.36 (4.94)	<.01	<.05	T
Instrumental	+	9.53 (4.90)	14.97 (6.14)	<.01	11.93 (5.42)	15.73 (5.86)	<.01	<.01	NS
Perceptions									
Interpersonal	+	10.54 (7.26)	10.34 (8.34)	NS	10.23 (7.23)	8.92 (7.63)	NS	NS	T
Intrapersonal	−	14.56 (3.68)	14.91 (3.29)	NS	13.13 (3.30)	12.49 (2.82)	NS	<.01	<.01
Communication	+	9.73 (3.38)	8.76 (3.71)	NS	9.82 (3.23)	8.76 (3.67)	NS	NS	NS
Fear of disease	−	2.19 (2.54)	1.66 (2.09)	NS	2.09 (2.24)	1.08 (1.51)	<.05	NS	<.05
Mood									
Camper self-report									
Positive	+	21.88 (5.09)	20.58 (5.02)	NS	22.41 (4.82)	22.50 (4.64)	NS	NS	<.01
Negative	−	8.03 (3.87)	8.98 (4.53)	NS	7.25 (3.94)	6.48 (4.04)	NS	NS	<.01
Parent report									
Positive	+	23.15 (4.27)	21.00 (3.61)	<.05	23.33 (3.68)	22.29 (4.15)	NS	NS	<.01
Negative	−	8.63 (4.12)	9.05 (3.69)	NS	7.47 (3.61)	6.55 (3.55)	NS	<.05	<.01

*Plus indicates positive; minus, negative; T, trend effect; and NS, not significant.

Table 5.—Effect of Perceived Adaptational Status on Outcome Measures*

Outcome Variable	Desired Direction of Change	Precamp, Mean (SD)			Postcamp, Mean (SD)			Precamp vs Postcamp Results, P	
		No	Yes	P	No	Yes	P	No	Yes
Medical knowledge									
Identification	+	11.69 (5.97)	12.43 (6.14)	NS	13.22 (6.62)	13.22 (5.86)	NS	<.05	T
Instrumental	+	11.63 (6.34)	12.70 (5.96)	NS	13.94 (5.88)	13.89 (5.81)	NS	<.01	T
Perceptions									
Interpersonal	+	7.70 (6.53)	12.56 (8.04)	<.01	7.58 (7.14)	11.32 (7.33)	<.05	NS	NS
Intrapersonal	−	14.43 (3.13)	14.83 (3.70)	NS	12.88 (3.18)	12.82 (3.07)	NS	<.01	<.01
Communication	+	10.15 (3.44)	8.63 (3.53)	<.05	9.37 (3.21)	9.38 (3.68)	NS	T†	T
Fear of disease	−	1.85 (2.28)	1.98 (2.42)	NS	1.78 (2.15)	1.48 (1.89)	NS	NS	T
Moods									
Camper self-report									
Positive	+	21.50 (5.14)	21.13 (5.11)	NS	23.27 (3.34)	22.03 (5.30)	NS	<.05	NS
Negative	−	7.93 (3.87)	9.01 (4.41)	NS	7.53 (3.59)	6.39 (4.28)	NS	NS	<.01
Parent report									
Positive	+	23.67 (3.11)	21.00 (4.41)	<.01	24.02 (3.14)	22.09 (4.09)	<.05	NS	<.05
Negative	−	8.00 (3.05)	9.86 (4.41)	<.05	6.35 (3.07)	7.44 (3.80)	NS	<.05	<.01

*Plus indicates positive; minus, negative; no, no adaptational problems; yes, adaptational problems; NS, not significant; and T, trend effect.
†Indicates trend in undesired direction.

was found beyond that related to age. That is, older siblings seem to understand the disease more fully than younger siblings regardless of the time since diagnosis; and, conversely within the age groupings, time since diagnosis did not significantly influence level of knowledge.

Comparison of precamp and postcamp assessments revealed that younger campers showed significant improvement in identification ($P<.05$) and instrumental understanding ($P<.01$); older campers made only minor gains in medical information.

Perception.–No precamp group differences emerged for any of the perception factors. After camp, older campers differed significantly ($P<.05$) from younger campers with reference to fear of disease. Comparison of precamp and postcamp assessments revealed that younger and older campers showed significant changes in the intrapersonal factor ($P<.01$), but only older campers reported a significant decrease in fear of disease ($P<.05$).

Mood.–The only significant precamp difference in mood was greater positive mood among younger campers as reported by parents. This difference disappeared at the time of postcamp testing. Precamp and postcamp results revealed significant desired changes in the positive and negative mood categories among the older campers, as reported by themselves ($P<.01$) and their parents ($P<.01$), and in negative mood among the younger campers as reported by their parents ($P<.05$).

Perceived Adaptational Status.—*Medical Knowledge.*—As shown in Table 5, neither precamp nor postcamp level of medical knowledge distinguished campers with and without adaptational problems. Comparison of precamp and postcamp assessments revealed a significant increase in medical knowledge among nonproblem campers as well as desirable trends toward greater knowledge among the campers experiencing adaptational difficulties.

Perception.—Precamp differences were found for the interpersonal and communication factors. Specifically, the nonproblem campers reported fewer concerns about relationships with others and better ability to discuss both cancer- and noncancer-related issues with others. Postcamp analysis revealed differences only for the interpersonal factor. Comparison of precamp and postcamp assessments revealed significant desirable changes in the intrapersonal factor (feelings of anger, sadness, and others) for both groups ($P<.01$) and a desirable trend affect for fear of disease among problem campers. The trend toward poorer communication found among nonproblem campers on the precamp and postcamp assessments represents the only undesirable change uncovered by any of the analyses.

Mood.—Precamp mood differences as rated by parents but not by campers were found between problem and nonproblem campers. Postcamp differences were found only for positive mood as reported by parents. Comparison of precamp and postcamp assessments revealed that nonproblem campers had significant desirable changes in positive mood by self-report ($P<.05$) and in negative mood by parent report ($P<.05$). Problem campers had significant changes in all mood categories ($P<.05$) except for positive mood as rated by campers, which was unchanged.

Previous Camp Experience.—As shown in Table 6, no precamp group differences were noted in any of the outcome variables when returning and new campers were compared. The only postcamp difference was greater ability to identify medical procedures noted among returning campers.

Medical Knowledge.—Comparison of precamp and postcamp assessments revealed that ability to describe medical procedures improved significantly among the returning campers ($P<.01$). Instrumental understanding improved among both new and returning campers ($P<.05$).

Table 6.—Effect of Previous Camp Experience on Outcome Measures*

Outcome Variable	Desired Direction of Changes	Precamp, Mean (SD)			Postcamp, Mean (SD)			Precamp vs Postcamp Results, P	
		Return	New	P	Return	New	P	Return	New
Medical knowledge									
Identification	+	13.24 (6.66)	11.21 (5.40)	NS	15.47 (6.00)	11.44 (5.72)	<.01	<.01	NS
Instrumental	+	13.17 (6.76)	11.29 (5.50)	NS	14.91 (5.95)	12.79 (5.78)	NS	<.05	<.05
Perceptions									
Interpersonal	+	9.22 (7.17)	11.48 (8.11)	NS	8.68 (7.29)	10.41 (7.49)	NS	NS	NS
Intrapersonal	−	15.03 (3.39)	14.47 (3.58)	NS	12.94 (2.82)	12.74 (3.33)	NS	<.05	<.01
Communication	+	9.63 (3.57)	8.98 (3.54)	NS	9.70 (3.37)	9.02 (3.56)	NS	NS	NS
Fear of disease	−	2.17 (2.59)	1.75 (2.13)	NS	1.96 (1.91)	1.33 (2.03)	NS	NS	NS
Moods									
Camper self-report									
Positive	+	20.63 (5.00)	21.80 (5.13)	NS	22.51 (4.89)	22.40 (4.60)	NS	<.05	NS
Negative	−	8.52 (4.38)	8.43 (4.07)	NS	6.98 (4.41)	6.82 (3.64)	NS	<.05	<.01
Parent report									
Positive	+	22.45 (3.81)	21.89 (4.35)	NS	22.41 (4.36)	23.21 (3.52)	NS	NS	<.05
Negative	−	8.55 (3.27)	9.47 (4.40)	NS	6.79 (3.82)	7.25 (3.42)	NS	<.01	<.01

*Plus indicates positive; minus, negative; return, returning camper; new, new camper; and NS, not significant.

Perception.—Comparison of precamp and postcamp assessments revealed that returning and new campers reported significant desired changes in the intrapersonal factor.

Mood.—Comparison of precamp and postcamp assessments revealed significant desired changes in mood as reported by campers and parents ($P<.05$) in almost all mood categories for both returning and new camper populations.

COMMENT

It has been suggested that specialized camps for children with cancer may not only be unnecessary, but may even be detrimental to participants by unduly focusing on the disease and its side effects.[14] However, a recent study investigating the effect of such programs provides evidence of their benefit.[6] Camping programs designed for other family members (eg, siblings) of children with cancer are rare. As has been the case with their sick brothers or sisters, it could be argued that involving siblings in an intensive experience structured around cancer-related issues might be overwhelming to the participants. However, the overall results of the current investigation support the efficacy of such a camp program and reveal no significant negative effects in any of the outcome measures studied. Indeed, desirable changes in medical knowledge, perceptions of disease influence, and mood found after camp indicate that the goals of the camping experience were reached and seemed to have a positive effect on the campers for at least as long as 3 months.

Medical Knowledge

With respect to medical knowledge, the camp seems to be most beneficial to younger campers who have more limited understanding and who may respond more favorably to the hands-on, concrete demonstrations used during these sessions. The smaller effects noted among older campers probably reflect "topping off," suggesting that more sophisticated types of instruction may be appropriate for this group. The value of repeated instruction is suggested by the finding that returning campers showed significant improvements in level of knowledge.

The lack of precamp differences in level of knowledge between problem and nonproblem campers was surprising because it is often assumed that lack of information may contribute to adaptational difficulties. Both groups of campers did, however, benefit from instruction.

Perceptions and Attitudes

Regardless of how the camper population is divided for analysis, the major consistent influence of the camp was on intrapersonal attitudes toward cancer (feelings of sadness and anger, preoccupation with the disease). This is not unexpected given the structure of the camp which focused on self-help strategies, peer support, and information giving. That is, family issues, such as those comprising the interpersonal and communication factors, were less likely to be influenced to any degree by an experience that excluded, for example, parents. The need for other kinds of approaches, either within or outside of the camp program, is highlighted by the significant differences in the interpersonal factor found between campers with and campers without problems. Before camp began, campers with problems clearly reported greater perceived disruption within the family and less ability to communicate. Although ability to communicate was enhanced at the postcamp reporting, perception about relationships within the family still distinguished the two groups. Thus, if this issue, which seems to be a major discriminator of siblings with adaptational problems, is to be addressed, it must be done through a program that is structured differently from the camp described here.

Moods

Campers' report of personal mood state did not distinguish any of the

groups either before or after camp. The decrease in self-report of negative mood noted for new, older, and problem campers after the camp was the only consistent change. By parent report, mood consistently distinguished problem from nonproblem campers when precamp testing occurred. However, parents reported significant desirable changes for positive and negative moods among new, older, and problem campers after camp. This last finding is consistent with and, thus, helps corroborate, the self-report changes noted above.

CONCLUSION

The camping experience we have described provided a positive recreational, informational, peer-support experience that was profitable for siblings aged 6 to 17 years. Siblings identified by their parents as having behavioral problems with onset since the diagnosis of the cancer seemed to benefit particularly from attendance at camp. The effects of the camp experience were sustained for at least the 3-month follow-up period and were evident to the campers and their parents.

The camp, however, has a number of limitations necessarily imposed by its short duration and design. For example, because the camp was not structured to include the entire family, little change in siblings' perceptions of interpersonal or communication issues within their families was found. Lack of substantial change in such areas should not be construed as a failure of the program, but rather as a realistic assessment of the limits of the camp's intent and sphere of influence. Other programs, whether conducted in a camp atmosphere or not, that address parent-child interaction, for example, need to be devised to compliment this particular program if interpersonal issues in the family are to be addressed effectively. Thus, this particular camp experience should be considered a successful component of, rather than a panacea for, a comprehensive program for enhancement of sibling adaptation to childhood cancer.

Common sense supports the notion that greater attention to the questions and other needs of siblings should be an integral part of the whole family approach to treatment of the child with cancer. The fact that camps and other types of community-supported programs have developed and flourished indicates that some families, at least, perceive their noncancer-affected children as needing more (or different) support services than are being provided at pediatric oncology centers. Are camp programs the best vehicle for providing such support? For some children (eg, those who feel uncomfortable in more formal settings), the answer is "yes."

For others, for probably a variety of reasons, the answer is "no." The concept of the camping experience as a worthwhile intervention for providing emotional support to children with cancer and their families have received widespread acclaim and support during this decade. The future will undoubtedly see another form of intervention that will gain similar popularity and support, and, perhaps, attract a somewhat different subset of participants to profit from what it has to offer. Although, clearly, camp is not for everyone, it should be reassuring to those who contribute time and money to such programs to know that those who do choose to participate gain something positive from the experience.

This research was supported by grants from the W. T. Grant Foundation (85-1037-85), New York, NY, and the American Cancer Society, Atlanta, Ga (Junior Faculty Research Award 127).

The authors would like to thank the siblings and families who participated in this study and the chairman (Mr Gary Mervis) and staff of Camp Good Days and Special Times Inc for their valuable assistance and dedication to the project. Those interested in more information regarding this sibling program should write to Camp Good Days and Special Times Inc, 100 White Spruce Blvd, Rochester, NY 14623.

References

1. Shields JM, Abrams P, Siegel S. An alternate health care setting with cancer: a residential summer camp. *Child Health Care*. 1985;13:135-138.
2. Robinson W. Summer camp for diabetics. *Nurs Mirror*. 1977;145:50-52.
3. Friedman CB. Kids with cancer go to camp. *Cancer News*. 1982;36:6-9.
4. Dasson ME. A chance to be normal again. *Cancer Nurs*. December 1982:453-459.
5. Nowicki S, Barnes J. Effects of a structured camp experience on locus of control in children. *J Genet Psychol*. 1971;48:21-30.
6. Smith KE, Gottlieb S, Gurwich DH, Blotcky AD. The impact of a summer camp experience on daily activity and family interaction among children with cancer. *J Pediatr Psychol*. 1987;12:533-542.
7. Duquin LH. Camp B&ST: help for the other victims of cancer. *Seventeen*. May 17, 1986:118.
8. Sahler OJ, Carpenter PJ. Developmental differences among siblings' perceptions of the pediatric cancer experience. *J Dev Behav Pediatr*. 1987;8:121.
9. Carpenter PJ, Sahler OJ. Sibling perception and adaptation to childhood cancer: conceptual and methodological considerations. *J Pediatr Psychol*. In press.
10. Sourkes B. Siblings of pediatric cancer patients. In: Kellerman J, ed. *Psychological Aspects of Childhood Cancer*. Springfield, Ill: Charles C Thomas Publisher; 1980:47-69.
11. Spinetta JJ. The siblings of the child with cancer. In: Spinetta JJ, Deasy-Spinetta P, eds. *Living With Childhood Cancer*. St Louis, Mo: CV Mosby Co; 1980:133-152.
12. Carpenter PJ. Parent involvement in preparing pediatric cancer patients for invasive medical procedures: a cognitive-behavioral approach. *Proc Am Soc Clin Oncol*. 1987;6:256.
13. Schwartz L, Eagle CJ. *Psychological Portraits of Children*. Lexington, Mass: Lexington Books, 1986.
14. Tebbi CK, Klemperer MR. Summer camp for children with cancer: is it necessary? *Candlelighters Foundation Newsletter*. 1981;5:3.

In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Placental Metastasis From Maternal Bronchial Oat Cell Carcinoma

Christian Delerive, MD; Florence Locquet; Ann Mallart, MD; Anne Janin, MD; Bernard Gosselin, MD (*Arch Pathol Lab Med*. 1989;113:556-558)

"OUCH"

For "minor league" injuries, there's a better choice than aspirin

When your 6- to 14-year-old patients need pain relief for minor injuries, Junior Strength TYLENOL® acetaminophen should be your first choice. Clinical studies have proven TYLENOL® to be every bit as effective as aspirin for pain relief,[1] with a superior safety profile.[2] Together with the recommended regimen of rest, ice, compression, and elevation, it's the better choice than aspirin for the pain of minor self-limiting injuries.[3]

Junior Strength TYLENOL® can also help reduce underdosing because children need only half as many 160 mg caplets as 80 mg chewables. They're coated for easier swallowing, too.

So next time a junior patient says "Ouch!", recommend local therapy for the inflammation, and make your first choice Junior Strength TYLENOL® acetaminophen for the pain.

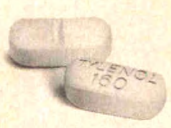
References: 1. Cooper SA: *Arch Intern Med* 1981;141:282–285. **2.** Aspirin or paracetamol? *Lancet* 1981;II:287–289. **3.** Senior RJ: *J Adolesc Health Care* 1986;7(suppl to No. 6):24S–30S.

JUNIOR STRENGTH

TYLENOL®

160 mg acetaminophen

COATED CAPLETS



First choice for pain relief in the 6–14 year old

© McN, 1988

McNeil Consumer Products Company
Fort Washington, PA 19034

McNEIL

Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio
Fredric Burg, MD, Philadelphia, Pa
Harold Levine, MPA, Galveston, Tex
Barbara Starfield, MD, Baltimore, Md
Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of parents and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—*We are often frustrated about parental understanding of the meaning of fever. Another problem is making productive use of our waiting rooms in terms of function and time. In this article, Robinson and colleagues show how both of these frustrations can be met. See if you can apply this to your practice.*—H.D.A.

The Impact of Fever Health Education on Clinic Utilization

J. Stephen Robinson, MD, PhD, MPH; Mei-Ling M. Schwartz, MPH;
Katherine S. Magwene, MPH; Saundra A. Krengel, LVN; Diane Tamburello, MPH

• We evaluated the ability of an office health education program to (1) increase parental knowledge about fever in children, (2) improve parental satisfaction with services, and (3) affect the number of fever-associated clinic visits. Randomly selected experimental and control groups differed only in that the former group viewed a slide-tape presentation. Testing of population samples before and after the presentation disclosed a highly significant improvement in knowledge about fever in the experimental population that persisted for almost 6 months. Monitoring of subsequent clinic visits revealed a 30% to 35% decrease in visits for fever and a 20% to 25% decrease in all visits for acute problems. These findings suggest that an audiovisual health education intervention can significantly improve patient confidence in managing fever as reflected by decreased clinic visits. This program is potentially useful in both the office and clinic in a health maintenance organization setting.

(*AJDC.* 1989;143:698-704)

The literature contains scant evidence supporting the effectiveness of health education in improving health care in the office. Reported experiences have met with mixed results.[1-6] In general, interventions utilizing solely verbal instruction have been shown to be unreliable for producing long-term behavioral change in parents.[7] In studies comparing a variety of educational approaches used for parent training, patients have consistently demonstrated the greatest gains in knowledge or skills when audiovisual materials were used, as compared with printed materials or verbal instruction.[8,9]

Consequently, there has been a recent emphasis on alternative approaches such as videotape programming. A recent American Academy of Pediatrics symposium on pediatric patient education that discussed the need for the pediatrician to increase his or her role in health education advocated videotapes for more effective communication and education.[10]

Media aids commonly used in patient education are frequently successful at increasing the learner's knowledge but often do not bring about the desired behavioral change. A well-designed, motivational media program should be able to do both.

The Child Health Advisory Talks project was undertaken to create a series of audiovisual education messages for parents that provide knowledge and skills in managing common childhood complaints such as fever, upper respiratory tract illness, ear problems, and gastrointestinal tract infections. Fever or high temperature is the most common complaint seen in our acute pediatric ambulatory care clinic, constituting 20% to 25% of all chief complaints. This is followed closely by cold/cough (22%), ear problems (21%), sore throats (14%), and vomiting/diarrhea (13%).

The videotaped messages were de-

Accepted for publication December 20, 1988.

From the Departments of Pediatrics (Dr Robinson and Ms Krengel) and Member Health Education (Mss Schwartz, Magwene, and Tamburello), Kaiser Permanente Medical Center, Panorama City, Calif.

Presented at the 13th World Conference on Health Education, Houston, Tex, August 29, 1988.

Reprint requests to Department of Member Health Education, Kaiser Permanente Medical Center, 13652 Cantara St, Panorama City, CA 91402 (Ms Schwartz).

signed to be viewed in clinic waiting rooms or as part of the well-baby clinic parent education program in our health maintenance organization (HMO). Each topic was developed using "interactional step-testing" with medical staff and parent focus groups. *Step-testing* is a term we coined to describe a technique wherein the parents themselves participate in determining the content via survey responses that indicate knowledge gaps, concerns, and behaviors. The final product is determined after multiple interactive focus group tests and modification at sequential steps to maximize comprehension and impact.

The present study was conducted to evaluate the effectiveness of an audiovisual presentation on fever, entitled "Fever in Children: Fears and Facts," at increasing parental knowledge about fever, confidence in managing fever at home, and satisfaction with health education services. In addition, we sought to determine the long-term effect on parental behavior. We hypothesized that improved confidence in managing fever at home and the diminution of "fever fears" should result in decreased clinic visits for fever.

SUBJECTS AND METHODS

Families were recruited into the study by a research assistant as they presented to the Pediatric After Hours Clinic. Eligibility required that a child be registered with a chief complaint of "fever" or "high temperature" and be less than 13 years of age. Qualified families who consented to participate were randomly assigned by family account number into the experimental group (even account number) or the control group (odd account number).

In the process of obtaining informed consent parent-subjects were asked to complete a form requesting identification data and information on education, occupation, ethnic background, and number of children. Families who did not provide complete demographic information or who were not fluent in English were not included. Both groups were treated exactly alike except that the experimental families were privately shown a 10-minute slide-tape on fever in a clinic office separate from the examination and waiting rooms before they saw the physician. This sequestering was necessary to limit exposure of the media aid to only the experimental families. Before leaving the clinic both groups were individually seen by a physician for their complaint and before departure they were given a fever pamphlet that reviewed all the major points covered in the slide-tape presentation. The research assistant answered any questions triggered by the educational materials. Parents were also told that they might receive a follow-up telephone call later in the year.

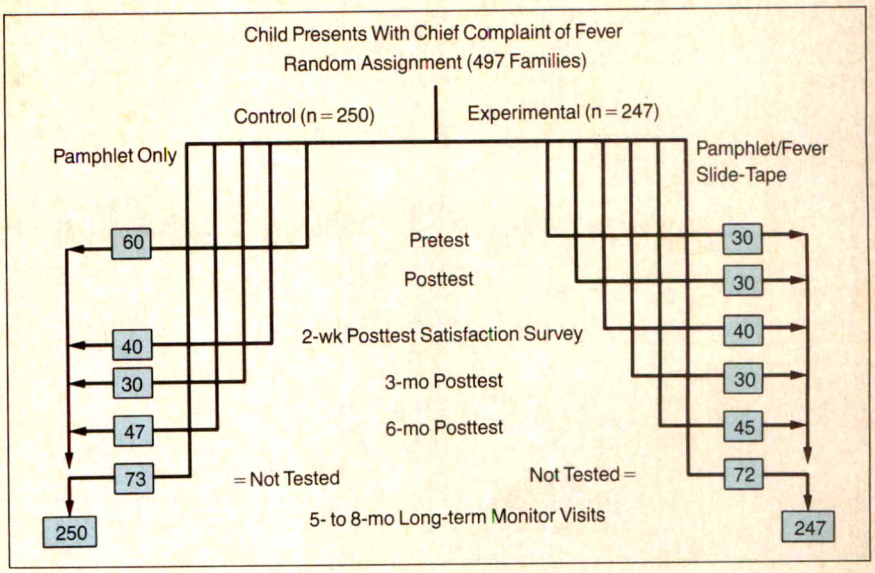


Fig 1.—Flow diagram of study design.

Clinic registration cards of all eligible children enrolled in each subject family were flagged to monitor clinic visits. Pediatric registration clerks were able to identify fever study patients making visits at any time on any day of the week. At that time the subject's parent was asked to check off only one complaint on a list of common pediatric problems, ie, the complaint that most prompted them to make their clinic visit. This method allowed us to measure approximately the parental anxiety about fever and to quantitate readily any subsequent clinic visits.

More than 500 families were registered over 8 months. The Green socioeconomic rating method[11] (updated in 1987, L. W. Green, DrPH, personal communication) was used to ensure comparability between groups.

The overall evaluation scheme is shown in Fig 1. At each designated interval, different family samples were tested to avoid the effects of repetitive testing of individual subjects. Families were randomly assigned to one of the six sample groups by order of presentation to the clinic. The groups were statistically large enough to ensure the validity of comparing single-tested samples with one another.

A 10-item questionnaire was developed to use throughout the study for surveying subject knowledge, attitudes, and practices regarding fever. Questions were true/false and multiple choice, allowing incorrect responses to be tallied easily. The number of incorrect responses served as a grade or score. The questionnaire was extensively pretested for reliability using more than 100 parent-subjects who were not included in the study. In addition, the questionnaire was constructed for ease in administration in both the clinic and over the telephone.

Thirty experimental parents completed a test questionnaire before viewing the fever slide-tape (pretest group). Another 30 subjects completed the test immediately after the viewing as a measure of the intervention's ability to confer new knowledge.

Sixty parent-subjects in the control group (equivalent to a pretest group) completed the same questionnaire during their visit. This sample number was chosen to ensure that an equal proportion of subjects were tested in each major group, thus balancing for testing

Table 1.—Demographic Characteristics of Study Population

	Experimental Families (n = 247)	Control Families (n = 250)
Mean (±SD) Socioeconomic score*	60.9 ± 0.6	61.1 ± 0.6
Ethnic background, %		
White	56.7	48.8
Hispanic	25.2	30.0
Black	8.1	10.4
Asian	9.2	9.2
Other	0.8	1.6
No. of children	510	503
No. of children per family	2.06	2.01

*Data were obtained by the Green technique.[11]

Table 2.—Fever Knowledge Retention*

	Group				
	Experimental		Control		
	Score†	SES‡	Score	SES	P
Pretest	5.97 ± 0.35 (n = 30)	60.9 ± 1.3	6.60 ± 0.28 (n = 60)	60.1 ± 1.0	Not significant
Immediate posttest	1.33 ± 0.28 (n = 30)	60.7 ± 1.5	6.60 ± 0.28 (n = 60)	60.1 ± 1.0	<.001
2-wk posttest	2.18 ± 0.31 (n = 40)	59.8 ± 1.3	4.75 ± 0.47 (n = 40)	62.0 ± 1.4	<.001
3-mo posttest	2.67 ± 0.39 (n = 30)	63.5 ± 1.4	4.93 ± 0.52 (n = 30)	60.9 ± 1.8	<.001
6-mo posttest	4.07 ± 0.42 (n = 45)§	63.3 ± 1.3	5.11 ± 0.38 (n = 47)§	61.9 ± 1.4	.070

*Values are the mean ± SD.
†Number of incorrect responses.
‡Socioeconomic scores (SESs) do not differ significantly between groups.
§Difference from pretest value significant at $P<.005$ by Student's t test.

effects. In all cases, whether experimental or control, the parents completed the test before seeing a physician or receiving the fever pamphlet.

Telephone follow-up interviews were conducted on different samples of the study population at 2 weeks (40 experimental subjects; 40 controls), 3 months (30 experimental subjects; 30 controls), and 6 months (47 experimental subjects; 45 controls) after the educational intervention. During these interviews unsolicited comments about the health education intervention were noted and the fever test questionnaire was administered. At the 2-week follow-up contact, a formal patient satisfaction survey was also conducted by telephone to assess patient satisfaction with services.

Evaluation of the intervention's long-term effects on behavior was measured by tallying patient revisit forms. Visits were easily delineated as being for fever, for other acute complaints, or appointments that did not involve an acute problem.

Patient revisits were tallied for almost 1 year. As almost 8 months were required to enroll everyone in the study, subjects were followed up for differing periods of time. All of the study families were followed up for at for least 2 months, 73.4% were followed up for 5 months, and 40.0% were followed up for a full 8 months.

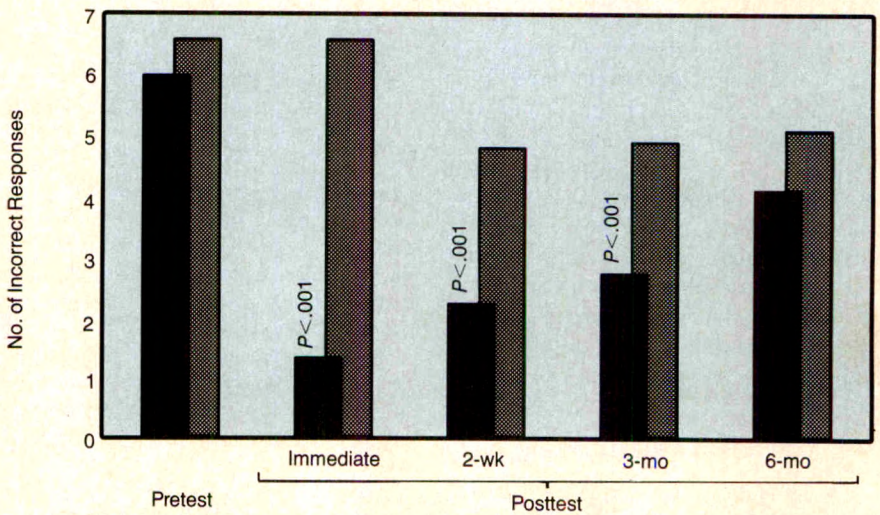


Fig 2.—Number of incorrect responses on test questionnaire within each study subgroup. P values reflect differences between experimental (solid bars) and control (shaded bars) subjects within each subgroup.

RESULTS

A total of 247 experimental and 250 control subject families were enrolled and followed up. Table 1 shows the demographic characteristics of each group. Differences were not statistically significant.

Scores representing the number of incorrect responses on the fever test questionnaire were compiled and averaged for each group (Table 2). There were no significant differences in pretest scores between the experimental and control groups. Those subjects viewing the fever slide-tape showed marked improvement in test scores immediately after the viewing, averaging slightly more than one wrong response, compared with the pretest average of approximately six wrong responses ($P<.001$). All groups were similar demographically, as shown by the socioeconomic status.

At 2 weeks and again at 3 months after the intervention, the experimental families continued to show significantly better posttest scores than did controls (Fig 2). This phenomenon faded by 6 months (score, 4.07 vs 5.11; difference significant at $P=.07$), although the average experimental score was still significantly better than the baseline pretest score ($P<.005$). The improvement in control posttest scores compared with the pretest scores is significant ($P<.005$) and probably reflects the impact of the pamphlet alone combined with the unintentional effects of being a "study" group. The socioeconomic status of paired groups was comparable in all cases.

Table 3 shows the cumulative number of visits for the families enrolled in the study for at least 8 months (101 experimental subjects and 98 controls). The data are sorted by visits for primary complaints of fever and visits for all acute problems including fever. In the first 30 days there were no visits for fever in the experimental group vs the control group (eight visits; $P<.005$). This effect decreased over time to a 35% difference by 7 months ($\chi^2=3.93$;

Table 3.—Cumulative Clinic Visits by Patients in Study for at Least 8 Months (N = 101/98)

	Visits for Fever				Total Visits for Acute Problems			
Days	Experimental Group	Control Group	Difference, %	P*	Experimental Group	Control Group	Difference, %	P
30	0	8	−100.0	<.005	25	44	−43.2	<.005
60	4	10	−60.0	NS	49	73	−32.9	<.005
90	9	16	−43.8	NS	72	98	−26.5	<.025
120	14	24	−41.7	<.05	88	123	−28.4	<.0025
150	15	26	−42.3	<.05	102	141	−27.7	<.001
180	18	28	−35.7	NS	110	158	−30.4	<.0005
210	20	31	−35.5	<.05†	121	174	−30.5	<.0001
240	22	32	−31.2	NS	139	186	−25.3	<.001‡

*NS indicates not significant.
†$\chi^2 = 3.93$.
‡$\chi^2 = 12.09$.

$P<.05$). A graph showing the cumulative number of visits with concern for fever grouped by time duration since enrollment in the study shows the data more clearly (Fig 3).

A tally of all visits for acute problems, including fever, yielded further significant results (Table 3, Fig 4). Eight months after the media intervention, experimental families had made 25.3% fewer visits to the clinic for acute complaints than control families (139 vs 186; $\chi^2 = 12.09$; $P<.001$).

The decision to follow up patients for 8 months to detect long-term behavior changes was empirical. Our patients make four or five clinic visits per year for acute problems. Since many of these visits occur in clusters during certain illnesses and seasons we assumed that it was rare for any one family to go more than 8 months without a clinic visit. Hence, 8 months was believed to be a period of time adequate to ensure that families had the opportunity to make at least one revisit for an acute problem.

Examination of a subpopulation of families that had been in the study for at least 5 months showed results similar to those seen with the 8-month subpopulation. With approximately 75% of the study population included in this 5-month subpopulation (n = 366; 181 experimental subjects and 185 controls),

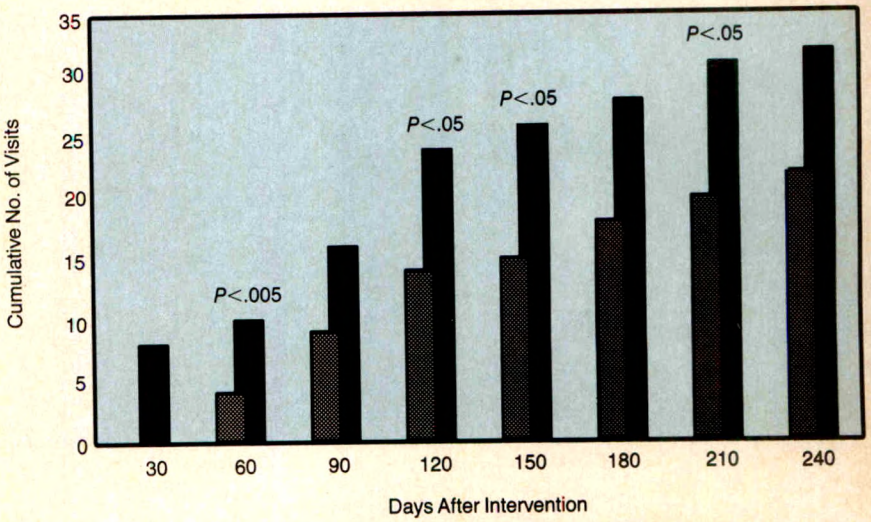


Fig 3.—Cumulative number of clinic visits with concern about fever distributed by time intervals after the health education intervention for those subjects in the study for at least 8 months. Shaded bars indicate experimental subjects (n = 101); solid bars, control subjects (n = 98).

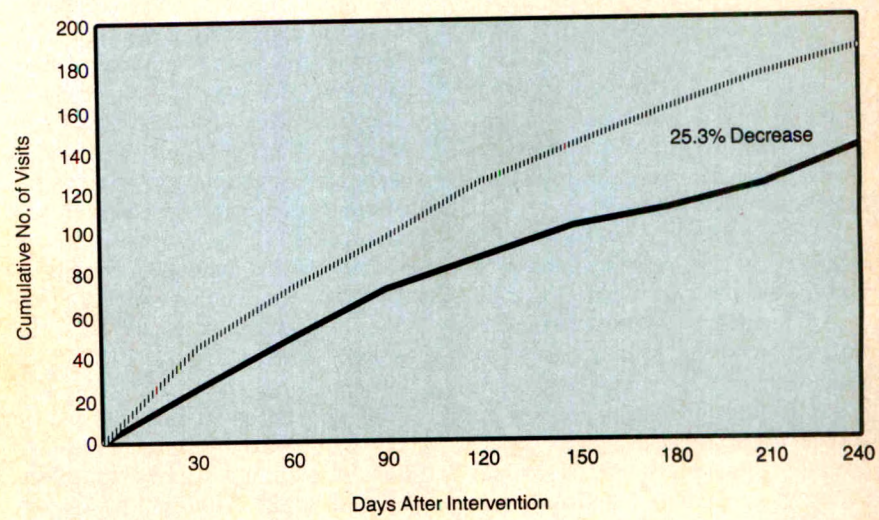


Fig 4.—Cumulative number of all clinic visits for acute problems distributed by time intervals after the health education intervention for those subjects in the study for at least 8 months. Solid line indicates experimental subjects; broken line, control subjects.

Table 4.—Cumulative Clinic Visits for Acute Problems by Patients in Study for at Least 5 Months (N = 181/185)

Days	No. of Visits: Experimental Group	No. of Visits: Control Group	Difference, %	P*
30	39	54	−27.8	<.05
60	70	87	−19.5	NS
90	104	123	−15.4	NS
120	124	160	−22.5	<.005
150	145	189	−23.3	<.005
180	157	210	−25.2	<.0005
210	169	231	−26.8	<.0001
240	187	244	−23.4	<.0005†

*NS indicates not significant.
†$\chi^2 = 13.70$.

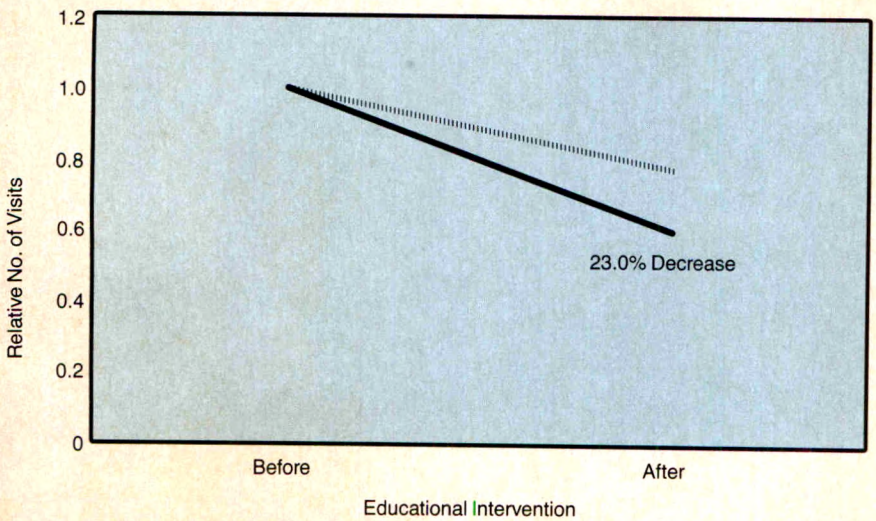


Fig 5.—Relative number of clinic visits for acute problems in the experimental group (solid line) vs the control group (broken line) 6 months before and 6 months after the educational intervention (there were 30 families in each group).

Table 5.—Medical Records Review of Clinic Visits

	Group: Experimental	Group: Control
No. of families	30	30
No. of patients	56	57
No. of visits for acute problems		
6 mo before education	148	141
6 mo after education	88*	109
No. of visits per family per year		
Before education	9.87	9.40
After education	5.87*	7.27
No. of visits per patient per year		
Before education	5.29	4.95
After education	3.14*	3.82
Change, %	−40.1	−22.7

*Difference between experimental and control significant at $P<.001$ by Student's paired t test.

there was a 23.4% decrease in total visits for acute problems ($\chi^2 = 13.70$; $P<.0005$) (Table 4).

A tally of the visits for nonacute problems showed that experimental families were just as likely to avail themselves of health services as were control families (64 vs 43).

To verify further that these tallied return visits were representative of actual visits and not an artifact of our data collection system, a formal medical records review was conducted on 30 experimental and 30 control families, selected randomly by computer, who had been in the study at least 8 months. A count of visits for acute problems made 6 months before and 6 months after the intervention revealed a decrease in visits in both groups (Table 5). When compared on the basis of number of visits per family per year, the experimental group rate dropped 40.1%, vs 22.7% for controls. This bilateral decrease is likely attributable to two additive factors: (1) the pamphlet had positive effects, and (2) the postinterventional 6-month period tended to encompass the spring and summer months more than the preinterventional 6-month interval. Clinic traffic tends to be lighter in the spring and summer months. When normalized for this phenomenon (Fig 5) the experimental group still demonstrated a significantly greater decrease (23.5%) in visits than the control (paired t test: $t = 3.612$; $P<.001$). This result compares very favorably with the decreases found from the tally of patient visits. The number of visits for nonacute problems was similar, indicating equal utilization of services by the two groups.

The patient satisfaction survey conducted at the 2-week follow-up telephone interview compared the responses of 40 experimental and 40 control parents (Table 6). As expected, all of the experimental interviewees recalled receiving some health education during their clinic visit, but only 80% of the controls remembered a health education program. This supports the notion that audiovisual media have a greater impact than written materials.[7-9] In addition, parents who saw the slide show were more likely to state that the health education material provided information they had not known before (73% vs 40%; $P<.02$). More interesting, however, was the finding that 2 weeks after the intervention, parents in the experimental group felt more confident in managing fever at home than did controls (88% vs 55%; $P<.002$).

Almost all of the experimental subjects wanted to see more audiovisual health education programs in the clinic, especially ones dealing with childhood disease management, skin disorders,

Table 6.—Satisfaction Survey

	Group, No. (%) of Subjects	
	Experimental (N=40)	Control (N=40)
Recall receiving health education	40/40 (100)	32/40 (80)
Pamphlet	38/40 (95)	32/32 (100)
Slide-tape	40/40 (100)	. . .
Read pamphlet	34/40 (85)	27/40 (68)
Felt information was new	27/40 (73)*	16/40 (40)
Felt information increased confidence	35/40 (88)†	22/40 (55)
Would like to see more audiovisual health education available‡	39/40 (95)	. . .

*Difference from control significant at $P<.02$ by χ^2.

†Difference from control significant at $P<.002$ by χ^2.

‡Subjects expressed a preference for receiving health education in clinic, pharmacy, and laboratory waiting rooms.

first aid, and child safety. All of the patients felt that the waiting room was a good setting for this endeavor and many suggested using such a scheme in the pharmacy and laboratory waiting rooms.

COMMENT

Health education is all too often given short shrift in the busy atmosphere of the pediatric clinic. The harried clinician is frequently so pressed that the delivery of health information is abbreviated and perfunctory. When this cursory instruction falls on the ears of a mother distracted by a screaming, anxious child, the effort becomes almost futile. Use of well-designed health education messages that present information in a clear, consistent, and entertaining manner seems an obvious improvement, especially in a setting that is more conducive to comprehension and recall.

Health education takes on a variety of forms, from the simple transmission of information to behavioral therapeutics. The former merely attempts to educate by providing facts (knowledge) about a particular subject whereas the latter attempts to induce long-term attitude and behavior changes. Increasing knowledge about an area of concern does not necessarily lead to a modification in behavior.[12]

The evaluation of the fever audiovisual health education message demonstrated the effectiveness of a well-prepared and tested audiovisual health education program. The fever slide-tape induced a significant retention of new information for up to 6 months after a single viewing. In addition, as has been shown by others,[8] the audiovisual message was superior to the written material containing the same information.

There are few well-designed studies that have been able to demonstrate significant changes as a result of an educational intervention, most of which tended to be short-term cognitive changes. A recent review of 13 studies describing educational interventions for childhood asthma found that the overall impact of these programs on school absences and utilization of health care services is probably small. Of those studies that showed some effect, only a small percentage used adequate controls and tests of statistical significance.[13]

The literature contains few reports of long-term maintenance of behavior change and even fewer reports of studies that used a randomized experimental control design. Probably the best-known example is the study by Morisky et al[5] on hypertensive patients in which health education in the form of interviews, home visits, and small group sessions resulted in a continuing positive effect on appointment keeping, weight control, and blood pressure control even after 5 years. Both the all-cause mortality rate and the hypertension-related mortality rate were decreased by half.

Programs aimed at achieving long-term behavior changes in such areas as household accident prevention,[2,6] child seat belt usage,[3,4] and dental health[14] have generally been less successful.

Measuring behavior change in a population poses difficulties since large numbers of subjects must usually be followed up for extended time periods to observe a significant shift. Our HMO setting provided us with a unique opportunity to carry out the required surveillance on a large patient population that had a comprehensive medical record system and was readily accessible for follow-up.

Results of the present study show that the fever health education program significantly affected the behavior of our experimental parent population. Our initial intentions at the outset of the Child Health Advisory Talks project were only to improve the quality of health education in the clinic and perhaps ease the education burden on the clinician. We were delighted to find that families who viewed the fever program only once made significantly fewer subsequent clinic visits with concern about fever than did the controls. We were even more pleased to discover that this effect carried over into the other acute problem areas where fever was not necessarily the major concern, eg, ear infections, sore throats, vomiting, and diarrhea. In retrospect this "ripple" effect makes sense. Fever is the most common complaint in our clinic, with ear infections, colds, sore throats, diarrhea, and vomiting accounting for the majority of the remaining complaints. Fever frequently accompanies these other conditions, so it would not be surprising that a reduction in concern about fever might carry over into a reduction in concern about associated problems.

The 20% to 25% reduction in clinic visits for acute problems among the experimental families for up to 8 months after the intervention confirms the long-term effectiveness of this particular health education program. Moreover, it demonstrates that health education can be cost-effective. In an HMO setting even a 5% to 10% decrease in clinic use can represent a savings of hundreds of thousands of dollars. Availability on a closed-circuit television system in all of the waiting areas could provide a substantial multiplier effect.

If the project had merely accomplished the single objective of improving patient satisfaction with services, it would have been deemed a success. Clearly, parents enjoyed the audiovisual health education format and welcomed more information. The perceived value of this intervention has encouraged us to move ahead with the production of the whole series of health messages dealing with other common

pediatric problems. These could be serialized on a single videotape for continuous viewing in the waiting room.

Since previous work has shown that distractions in the waiting room itself can diminish the impact of audiovisual programs,[15] the fever message (converted into a videotape format) was evaluated in the waiting room setting. Thirty-one parents who had seen the video while waiting completed the test questionnaire administered in the study. The mean (±SD) score was 1.58±0.29 wrong responses. This compares very favorably with the immediate posttest results obtained during the study (1.33 wrong responses) when parents were sequestered privately in a clinic office without distractions. When interspersed with other health education messages, the program can be designed to repeat automatically at chosen time intervals depending on the average waiting time. The effects of multiple viewing will likely enhance the impact by reinforcing the message and, with an average of eight or nine visits per family per year, there will be adequate opportunity for parents to view the same videotape on several occasions.

Our findings compare favorably with those of an earlier prospective study on efforts to educate parents in the office about fever and its management at home.[1] In that study 53 parents attended a 20-minute educational interview session on fever and 2 months later received printed materials for reinforcement. Compared with an equal number of controls, there was a dramatic decrease in inappropriate telephone calls regarding fever, inappropriate office visits, and the use of antipyretics for afebrile children 4 months after the intervention.

These results are not directly comparable with ours since different behavioral change criteria were measured. In both situations, however, close attention was paid to creation of the health education message relying heavily on knowledge-attitudes-practices surveys. The interactional step-testing technique used for developing our fever slide-tape, in addition, relied on focus-group testing at various stages of production. Both relied on alternative delivery techniques like interview sessions or audiovisual media aids. We were pleased to find that our automated audiovisual waiting room interventions were successful since the utilization of health educator interviews and mailed written material is very resource-intensive and not at all practical in an HMO setting.

The present study demonstrates that well-designed audiovisual aids such as the fever education program developed in the Child Health Advisory Talks project can not only increase knowledge and improve parental confidence at managing fever at home, but can make a sizable contribution to health cost savings by decreasing clinic utilization.

This study was funded by a research grant from the Southern California Permanente Medical Group, Pasadena.

The authors are grateful to S. Michael Marcy, MD, for his support and review of the manuscript, and to Stephen Beebe of Kaiser-Permanente Audiovisual Services for his assistance.

References

1. Casey R, McMahon F, McCormick M, Pasquariello PS, Zavod W, King FH. Fever therapy: an intervention for parents. *Pediatrics.* 1984;73:600-605.

2. Dershewitz RA, Williamson JW. Prevention of childhood household injuries: a controlled clinical trial. *Am J Public Health.* 1977;67:1148-1153.

3. Hletko PJ, Robin SS, Hletko JD, Stone MS. Infant safety seat use: reaching the hard to reach. *AJDC.* 1987;141:1301-1304.

4. Macknin ML, Gustafson C, Gassman J, Barich D. Office education by pediatricians to increase seat belt use. *AJDC.* 1987;141:1305-1307.

5. Morisky DE, Levine DM, Green LH, Shapiro S, Russell RP, Smith CR. Five-year blood pressure control and mortality following health education for hypertensive patients. *Am J Public Health.* 1983;73:153-162.

6. Schlesinger ER, Dickson DG, Westaby J, Lowen L, Logrillo VM, Maiwald AA. A controlled study of health education in accident prevention. *AJDC.* 1966;111:490-496.

7. O'Dell SL, Mahoney ND, Horton WG, Turner PE. Media-assisted parent training: alternative models. *Behav Ther.* 1979;10: 103-110.

8. Nay WR. A systematic comparison of instructional techniques for parents. *Behav Ther.* 1976;6:14-21.

9. Webster-Stratton C. Videotape modeling: a method of parent education. *J Clin Child Psychology.* Summer 1981:93-98.

10. Fulginiti VA. Role of the pediatrician in patient education. *Pediatrics.* 1984;74(suppl):914-916.

11. Green LW: Manual for scoring socioeconomic status for research on health behavior. *Public Health Rep.* 1970;70:815-824.

12. Green LW: Educational strategies to improve compliance with therapeutic and preventive regimens: the recent evidence. In: Haynes RB, Taylor DW, Sackett DL, eds. *Compliance in Health Care.* Baltimore, Md: Johns Hopkins University Press; 1979:157-173.

13. Bauchner HC, Howland J, Adair R. The impact of pediatric asthma education on morbidity: assessing the evidence. *AJDC.* 1988;142:398-399.

14. Lund AK, Kegeles SS, Weisenberg M. Motivational techniques for increasing acceptance of preventive health measures. *Med Care.* 1977; 15:678-692.

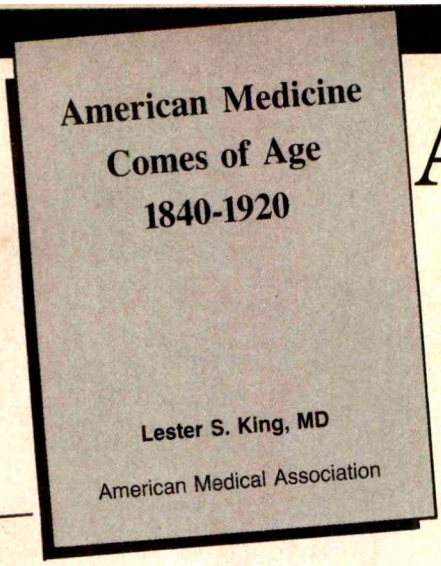
15. Kleemeier CP, Hazzard AP. Videotaped parent education in pediatric waiting rooms. *Patient Educ Counseling.* 1983;6:122-124.

In Other AMA Journals

ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY

Extensive Variations in Nasal Mucosa in Infants With and Without Recurrent Acute Otitis Media: A Scanning Electron-Microscopic Study

Finn Jorgensen, MD; Bjorn Petruson, MD; Hans-Arne Hansson, MD (*Arch Otolaryngol Head Neck Surg.* 1989;115:571-580)



Presenting...

American Medicine Comes of Age 1840-1920

The collected essays marking the centennial celebration of *The Journal of the American Medical Association.*

George D. Lundberg, MD
Editor
The Journal of the American Medical Association

On July 14, 1983, *The Journal of the American Medical Association* celebrated its 100th birthday. I had the great good fortune of being JAMA's editor during its centennial celebration. As we planned the celebration, many suggestions of appropriate activities were offered by the staff, the editorial board, and others. Among these was the idea that we publish original articles about the history of medicine in the United States before and during the life of *The Journal*.

Lester S. King, MD, the author of these fascinating historical vignettes, is no stranger to *Journal* readers. In recent years, he has served as editor of the book review column and of the annual "book issues" of *The Journal*. His knowledge and expertise in medical history are widely respected and make this commemorative edition a fitting tribute to the 100th birthday of *The Journal*.

I wish to extend my thanks to Dr. King for his achievement. I hope you will take advantage of this opportunity to share in the birthday celebration for *The Journal*.

George D. Lundberg, MD

Table of Contents

- The British Background for American Medicine
- Medical Education: The Early Phases
- Medical Sects and Their Influence
- The Founding of the American Medical Association
- The 'Old Code' of Medical Ethics and Some Problems It Had to Face
- Medical Education: The AMA Surveys the Problems
- The Painfully Slow Progress in Medical Education
- Germ Theory and Its Influence
- The AMA Gets a New Code of Ethics
- The Changing Scene
- Medicine Seeks to Be 'Scientific'
- Clinical Laboratories Become Important, 1870-1900
- The Founding of *JAMA*, 1883
- Medical Journalism, 1847-1883
- Clinical Science Gets Enthroned: Part I
- Clinical Science Gets Enthroned: Part II
- Medical Education: Elitism and Reform
- Medical Education: The Problems Intensify
- Medical Education: The Decade of Massive Change
- The Flexner Report of 1910
- Medical Practice: Specialization
- Medical Practice: Making a Living
- The Automobile Makes an Impact
- The Continuity of History

Format: 8⅛" × 10¾", 115 pages, detailed bibliographic notes, soft bound, ISBN 0-89970-177-9

Order Form

To order by phone with Visa or MasterCard, call toll free 1-800-621-8335. In Illinois call collect 312-645-4987.

Or complete and mail to . . .
Book & Pamphlet Fulfillment, OP-184
American Medical Association
P.O. Box 10946
Chicago, IL 60610-0946

Name
Address
City
State Zip

____ Copies @ $11.00 each $____
Less 20% AMA Members $____
Plus appropriate Sales Tax for residents of CA, DC, IL & NY $____
TOTAL . . . . . $____

☐ Enclosed is my check payable to the American Medical Association
☐ MasterCard ☐ Visa

Card No.
Expiration Date Phone
Cardholder signature

- Please allow 4-6 weeks for delivery.
- Prices subject to change without notice
- Quality discounts – 312-280-7168.

The Author
Lester S. King, MD

Dr. King's other books on medical history and philosophy include: *The Growth of Medical Thought* (1963), *The Road to Medical Enlightenment* (1970), *The Philosophy of Medicine* (1978), *Medical Thinking: A Historical Preface* (1982).

To add a copy of this special collection of essays to your personal library, mail the order certificate at the left.

Neurological and Developmental Findings in Children With Cataracts

Michael G. Pike, MA, MRCP; James E. Jan, MD, FRCPC; Peter K. H. Wong, MD, FRCPC

• Ninety-seven children who were born between 1954 and 1986 and presented to the Visually Impaired Program of British Columbia's Children's Hospital, Vancouver, Canada, with a primary ophthalmologic diagnosis of cataracts, were assessed neurologically, ophthalmologically, audiologically, and developmentally. Causal factors included prenatal infection (35 cases), hereditary cataracts (22 cases), various syndromes and metabolic disorders (9 cases), trauma (1 case), and unknown (30 cases). Ninety children were diagnosed to have congenital cataracts while 7 acquired them. Findings indicated that prenatal infection continues to be a cause of infantile cataracts, despite rubella immunization; that prematurity is not, as has been stated in the past, a cause of infantile cataract; and that careful neurological, audiological, and developmental examination is vital in the assessment of likely causes of this condition.

(*AJDC*. 1989;143:706-710)

Congenital legal blindness occurs in four of 10 000 births and bilateral cataracts, being the third most common ocular abnormality, are seen in 19% of these children.[1] Congenital or acquired infantile cataracts have been reviewed by a number of authors, mainly ophthalmologists, in terms of causes,[2-7] and of ophthalmologic management and visual outcome.[8-10] By contrast, cataracts have rarely been discussed in the pediatric literature, yet the diagnosis of cause is most often the responsibility of pediatricians. Furthermore, "systemic," neurologic, and developmental features of children with cataracts have not been, to our knowledge, specifically reviewed before and these all-important features form the basis of the present study.

Accepted for publication January 1, 1989.

From the Department of Paediatrics, Division of Paediatric Neurology, University of British Columbia, Visually Impaired Program, Children's Hospital, Vancouver, Canada.

Presented at the Canadian Congress of Neurological Sciences, Quebec, Quebec, Canada, June 16-18, 1988.

Reprint requests to Visually Impaired Program, British Columbia Children's Hospital, 4480 Oak St, Vancouver, British Columbia V6H 3V4, Canada (Dr Jan).

PATIENTS AND METHODS

The study population includes children with a primary ophthalmologic diagnosis of bilateral cataracts who were assessed at the Visually Impaired Program at the British Columbia's Children's Hospital, Vancouver, Canada, since its inception in 1970. Visually impaired and blind children who reside in British Columbia are referred to the program for multidisciplinary evaluations and developmental management. The study group therefore includes the majority of children from British Columbia with cataracts producing legal blindness, or slightly better vision, during the period examined. Patients with unilateral eye defects, with cataracts secondary to other ocular disorders, and whose visual outcome after surgery was good, were excluded. The influence of migration to and from the province and the changing referral patterns have not been taken into account. Therefore, this is a highly selected clinical experience and not an epidemiological study.

The referral of these children and the integration of services they received were facilitated by the Canadian National Institute for the Blind. All children were evaluated by a multidisciplinary team that included a pediatric neurologist, a pediatric ophthalmologist, a developmental psychologist, a speech pathologist, a physiotherapist, and an audiologist. Other specialists were involved in individual cases. A proportion had chromosomal, biochemical, metabolic, neuroradiological, and electrophysiological investigations performed as and when these were indicated on clinical grounds.

The records of all these children were assessed retrospectively, with particular reference to the family history; prenatal, perinatal and medical histories; age at diagnosis; age at and nature of treatment; neurological, audiological, and developmental assessment; and, finally, visual outcome.

RESULTS

Ninety-seven children with bilateral cataracts, born between 1954 and 1986, have been studied. The mean age at the time of their multidisciplinary assessment was 9.2 years (range, 6 months to 20 years); there were 46 boys and 51 girls. Eighty-seven children were born within British Columbia and 7 outside the province. Place of birth was not recorded for 3 children.

Age at Diagnosis

Sixty-seven children were diagnosed within the first 6 months of life and 3 between age 7 and 18 months. Nystagmus was present in all these patients and their visual loss was therefore considered to be congenital. In 7 children the cataracts were diagnosed after the age of 18 months: 3 were of unknown cause, 1 had congenital rubella, 1 had aldolase A deficiency (a metabolic disorder in which cataracts develop over time), 1 had recessively inherited cataracts, and 1 child with severe mental retardation acquired traumatic cataracts after prolonged and severe head banging. However, they all had nystagmus; therefore, their visual loss was congenital or was acquired under the age of 1 year. The exact age of diagnosis was unclear for 20 children. There was no significant change in age at diagnosis over the period studied. Most frequently the parents were the first to suspect "the eye problems." The peak time of diagnosis was between 2 and 3 months of age.

Causes

It is well recognized that children with cataracts can be divided into those in whom accompanying clinical features or test findings identify a "systemic" condition or syndrome of which their

cataracts form a part, and those in whom cataracts present as an isolated finding. Thus, for the purposes of analysis, the patients were allocated to the following five groups by cause: congenital infection (36%), unknown (31%), hereditary cataracts (23%), syndromes and metabolic disorders (9%), and traumatic (1%) (Fig 1). Although some of the syndromes and metabolic disorders were genetic, hereditary cataracts were listed separately because they are well known ophthalmological entities.

The largest group, containing 35 individuals (14 boys and 21 girls), had cataracts due to intrauterine infection. Of these, 31 were due to congenital rubella. The remaining 4 children who were diagnosed to have a prenatal infection on clinical grounds were extensively investigated, but the results were inconclusive with the exception of 1 child in whom Ebstein-Barr virus was implicated. Since the middle 1970s, only 6 children have been seen in our program with the diagnosis of congenital rubella syndrome. There was known rubella contact during five pregnancies. Two mothers, a recent immigrant from Asia and a European-born woman with a disturbed social background, were not immunized. Two others also were not immunized, but they refused abortion after the rubella exposure. The last two mothers were immunized, yet each gave birth to a child with congenital rubella syndrome. Their immunological status was extensively investigated and was found to be aberrant.

Family history indicated dominant inheritance in 20 children (9 boys and 11 girls). Their parents had ophthalmological examinations at the time of their children's assessments, but the grandparents' ocular disorders were diagnosed by history only because in most cases they lived far away or were deceased. Twenty of their parents had cataracts with nystagmus compared with only nine of their grandparents, indicating a spontaneous mutation rate of slightly over 50%. Recessive inheritance was diagnosed by geneticists in 2 children (both girls). Their parents had normal ophthalmological examination findings. Thirty others (19 boys and 11 girls) had cataracts of unknown cause. Of the remaining 10 children, 3 had Down syndrome, 2 had Lowe's syndrome, 1 had Hallermann-Streiff syndrome, 1 had trichothiodystrophy, 1 had aldolase A deficiency, 1 had an ocular syndrome in which cataracts, aniridia, and optic nerve and foveal hypoplasia occurred together, and 1 child, mentioned above, acquired traumatic cataracts from prolonged head banging.

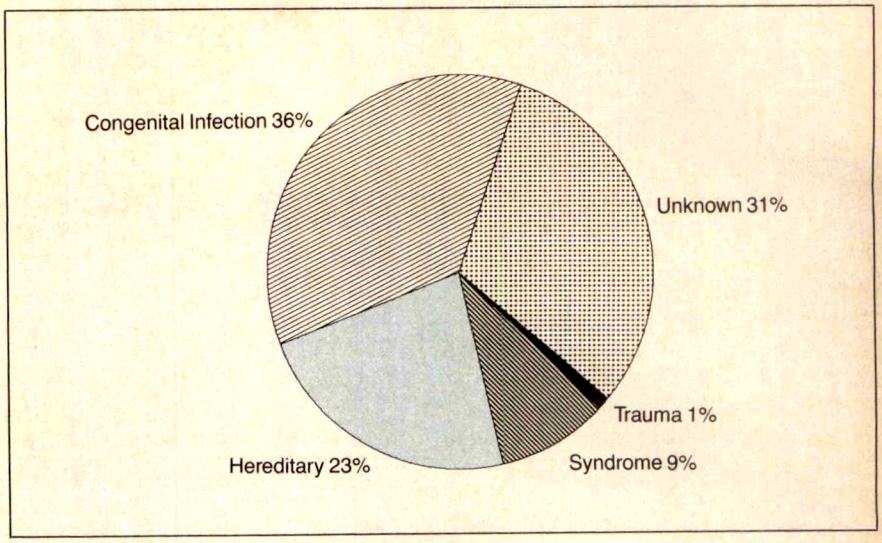


Fig 1.—Subgroups divided according to cause.

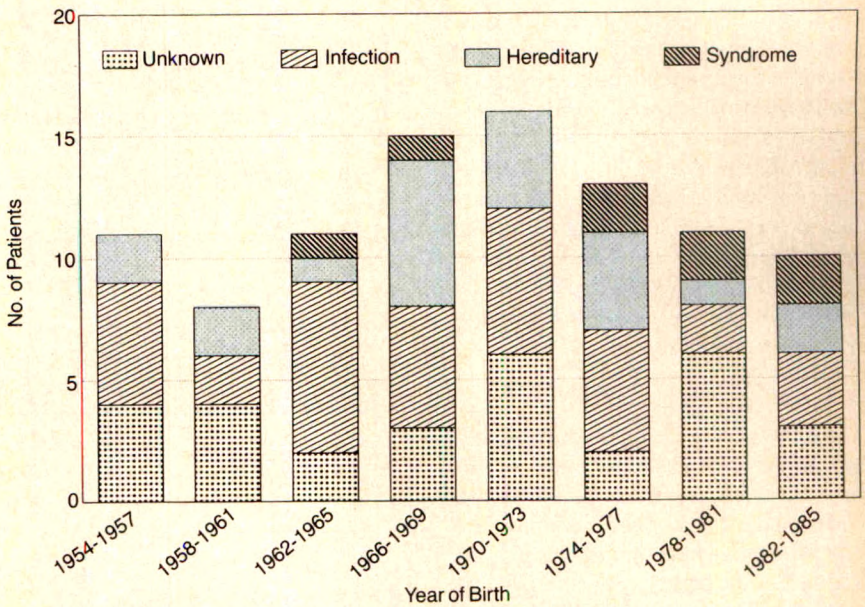


Fig 2.—Distribution of patients with cataracts of different subgroups according to cause by year of birth (n = 95; patient with traumatic cataracts and patient born in 1986 are not included).

Distribution Over Time

The distribution of date of birth for these patients as a whole and in their subgroups by cause was examined (Fig 2).

Prenatal and Perinatal Factors

The pregnancy and perinatal period were reviewed in all infants for significant abnormalities and these are shown in Table 1. Abnormalities of pregnancy that were recorded as significant included rubella or other specific maternal infections, vaginal bleeding, toxemia, gestational diabetes, ingestion of potential toxins or teratogens, placental dysfunction, poor fetal growth, and reduced fetal movement. Perinatal abnormalities included fetal distress, neona-

tal resuscitation measures lasting more than 5 minutes, feeding difficulties in the first days of life, severe irritability, seizures, hypoglycemia, hypocalcemia, septicemia, severe jaundice, and intraventricular hemorrhage.

Only 6 of 31 children with "unknown" cataracts had prenatal and perinatal abnormalities. (Table 2). Gestational age at delivery was available for 26 of these children and in no case was before 37 weeks of gestation. Birth weight was available for 24 children, of whom 3 had a birth weight below 2500 g, the lowest birth weight being 2180 g.

Neurological Assessment

The children's neurological examination findings were classified as normal, borderline, or abnormal. Borderline examination findings included mild hypotonia or mild incoordination, both common and nonpathological findings in visually impaired children.[11] Sensorineural hearing loss was considered separately as, when mild, this was not always apparent even on careful neurological examination. Abnormal neurological examination findings included unequivocally abnormal findings, such as spasticity, hemiplegia, and ataxia. The results for each category by cause are shown in Table 3.

Psychological Assessment

Eighty-four children were assessed psychologically. The others were either too young for useful assessment to be performed, or were deaf and blind. The psychological evaluation of visually impaired children is complex and it is described elsewhere.[12] Specific learning disabilities were present in 19 children. Mental retardation (IQ <70) was present in 25 children. Table 4 shows the distribution of mental retardation in relation to category by cause. Children without additional handicaps, even if severely visually impaired, tended to do well in their physical and emotional development, in their education and vocation, in contrast to the multihandicapped, who were an enormous burden on society and on the resources of their families.

Audiological Assessment

Hearing was formally assessed in 96 children by audiologists, often on several occasions. Sensorineural deafness of some degree was present in 30 children of whom the majority had suffered congenital infection (Table 5).

Table 1.—Prenatal and Perinatal Abnormalities

Cause (n=97)	No. of Patients: Abnormality of Pregnancy	Abnormality of Perinatal Period	No Abnormality
Unknown (n=30)	4	4	24
Congenital infection (n=35)	31	12	3
Hereditary (n=22)	1	1	20
Syndrome/metabolic (n=9)	2	1	6
Trauma (n=1)	0	0	1

Table 2.—Prenatal and Perinatal Abnormalities in Children With Unknown Cataracts

Patient	Abnormalities of Pregnancy	Perinatal Abnormalities
1	Toxemia, gestational diabetes, maternal arthritis	Fetal distress, hypoglycemia, hypocalcemia, thrombocytopenia, feeding difficulty, respiratory distress
2	Vaginal bleeding in first trimester, toxemia	None
3	Ingestion of fertility drug after conception	None
4	Placental dysfunction, reduced fetal movements	Feeding difficulty, hypoglycemia
5	Normal	Fetal distress, severe irritability, meconium
6	Normal	Prolonged resuscitation, seizures

Table 3.—Neurological Findings

Cause (n=96)*	Neurological Examination Findings: Normal	Borderline	Abnormal
Unknown (n=30)	16	7	7
Congenital infection (n=34)	3	11	20
Hereditary (n=22)	15	7	0
Syndrome/metabolic (n=9)	2	3	4
Trauma (n=1)	0	0	1

*Numbers of patients indicate number evaluated.

Epilepsy and Congenital Heart Disease

Six children had epilepsy—3 from the unknown causes group, 2 of those with congenital infection, and 1 with traumatic cataracts. Seventeen patients had congenital heart disease, of whom 16 came from the congenital infection group and 1 had cataracts of unknown cause. The latter patient also had sensorineural deafness and may therefore represent a case of undiagnosed congenital infection.

Ophthalmic Treatment and Visual Outcome

All but 11 children had surgical treatment. The mean age of the patients at surgery on the first eye was 11.9 months

Table 4.—Psychological Evaluation

Cause (n=84)*	Mental Retardation
Unknown (n=27)	3
Congenital infection (n=29)	14
Hereditary (n=21)	1†
Syndrome/metabolic (n=6)	5
Trauma (n=1)	1

*Numbers of patients indicate number evaluated.

†One child was mentally retarded because of emotional and environmental deprivation.

Table 5.—Audiological Assessment

Cause (n=96)*	Sensorineural Deafness
Unknown (n=30)	4
Congenital infection (n=35)	26
Hereditary (n=21)	0
Syndrome/metabolic (n=9)	0
Trauma (n=1)	0

*Numbers of patients indicate number evaluated.

(range, 1 month to 150 months) and for the second eye was 13.8 months (range, 1 month to 150 months). The surgical approach, complications, and subsequent ophthalmic management of patients were beyond the scope of this study.

Visual acuity was assessed by standard recognition acuity charts in 96 patients and was categorized as "worse than 20/100," "worse than 20/200," "worse than 20/400," and "light perception only to no vision"—all categories referring to the acuity of the better eye. Table 6 shows the distribution of visual acuity in relation to cause. Because the study population represented a highly selected group of children with cataracts, the analysis of visual outcome in relation to multiple factors was not done.

Medical Investigations and Genetic Advice

Almost all children had already been examined by pediatricians before they were referred to the Visually Impaired Program. In the majority of instances these investigations were felt to be adequate. On the other hand, genetic advice for the families of children with "unknown" cataracts in most instances either was not given or was inaccurate.

Table 6.—Visual Acuity in the Better Eye

Cause (n=96)	Visual Acuity <20/100	<20/200	<20/400	Light Perception No Vision
Unknown	10	13	3	4
Congenital infection	8	18	7	2
Hereditary*	7	14	0	0
Syndrome/metabolic	1	6	1	1
Trauma	0	0	0	1
Total	**26**	**51**	**11**	**8**

*The visual acuity of a child with recessively inherited cataracts could not be determined accurately.

COMMENT

This study population of children with cataracts is a highly selective one, because they were referred to an agency working with visually impaired and blind children, due to their poor visual outcome. Nevertheless, their medical and neurologic analyses reveal several interesting findings.

In North American children, severe visual loss from congenital cataracts is relatively uncommon and is even less frequent due to acquired cataracts. Therefore, considering the infrequency, the patient population analyzed here is large. The majority of congenital cataracts causing visual impairment are diagnosed during the first 6 months of life, but only rarely immediately after birth. This is a problem, because early treatment of certain cataracts is crucial in preventing visual loss.[13]

During the last 10 years prenatal infection has moved from first place to second and now the four most common causes of cataracts are "unknown," "prenatal infection," "hereditary," and "systemic syndromes, including metabolic disorders" in decreasing frequency. Congenital infection, predominantly by rubella virus, is not entirely eradicated and has remained a cause of childhood cataracts in the 1970s and early 1980s. This reflects an inadequate immunization rate and an abnormal response to the live attenuated virus.[14] Immunization programs should be able to further reduce the prevalence of congenital rubella syndrome.[15]

The repeated evaluations of our patients revealed that children without additional handicaps, even if severely visually impaired or blind, tended to do well in their development, education, and vocation. On the other hand, multihandicapped children, especially those with prenatal infections and syndromes, were an enormous burden on the resources of the families and society. The prevention of just one or two cases of congenital infection could have saved millions of dollars.

A number of early authors[16-18] have commented on prematurity as a cause of permanent infantile cataracts. Others[5] have not clearly distinguished between prematurity and low birth weight in their discussion of cause. The roles of perinatal asphyxia, hypoglycemia and hypocalcemia, all suggested as causative agents by various authors, remain less clear.[5,19-22] The idea that prematurity by itself can cause cataracts still lingers on.[23] In fact, Jay[24] in 1976 considered prematurity and perinatal difficulties one of the three major causative factors in the development of childhood cataracts. The observations that in our group of 26 children with unknown cataracts and with known gestational age at birth, not a single child was born before 37 weeks' gestation makes the hypothesis of prematurity as a cause extremely unlikely. Perinatal difficulties more frequently occur where there has been a preceding maternal or fetal abnormality which, in itself, may predispose both to perinatal illness and to congenital cataracts. However, if the perinatal events themselves play a role in the pathogenesis of cataracts, it is a small one, because of the 18 children who experienced perinatal problems, 14 had cataracts for other reasons. The remaining 4 patients had cataracts of unknown cause, and in these there is a possibility that perinatal illness is relevant. However, it is noteworthy that in 2 of these 4 children there were also clear prenatal abnormalities,

leaving only 2 children of 97 in whom perinatal factors alone were associated with the subsequent development of cataracts. It seems, therefore, that a stormy perinatal course rarely, if ever, causes cataracts and should certainly never be accepted as the explanation until other more common causes have been excluded.

The parents and siblings of normal children with unknown cataracts should have careful ophthalmological examination because there is often variable expressivity and penetrance of autosomal dominant cataracts.[4] The neurological and audiological examinations as indicators of cause are extremely important for accurate genetic advice. No patient in our study with established, dominantly inherited cataracts had an additional handicap. In contrast, the vast majority of children with cataracts due to prenatal infections, syndromes, and other causes had neurological and audiological abnormalities. The spontaneous mutation rate of indominantly inherited cataracts has been estimated at 50%[4] although in our study the proportion of unaffected grandparents suggests that it may be slightly higher. Therefore, there should be approximately the same number of children with dominantly inherited cataracts as children with unknown cataracts, but without affected parents. That is to say, in our study, approximately 20 of unknown cataracts would be expected to represent new, dominant mutations. In fact, 21 children with unknown cataracts had essentially normal neurological and audiological examination findings. This suggests that indeed the spontaneous mutation rate of dominant cataracts is around 50% and the vast majority of children with unknown congenital cataracts who are neurologically and audiologically normal fall into the newly mutated dominant group. In those children with congenital unknown cataracts who have additional handicaps, the hereditary cause should not be readily accepted. On the other hand, individuals with congenital cataracts, but without handicaps, will have a 50% chance of transmitting this ocular disorder to each of their offspring.

References

1. Robinson GC, Jan JE, Kinnis C. Congenital ocular blindness in children 1945 to 1984. *AJDC*. 1987;141:1321-1324.
2. Wilson WA. Congenital cataracts: a review of 72 cases including the use of enzymatic zonulysis in 15 patients. *Arch Ophthalmol*. 1962;67:143-147.
3. Harley JD, Hertzberg R. Etiology of cataracts in childhood. *Lancet*. 1965;1:1084-1086.
4. Fraser GR, Friedmann AI. *The Causes of Blindness in Childhood*. Baltimore, Md: The Johns Hopkins Press; 1967.
5. Merin S, Crawford JS. The etiology of congenital cataracts: a survey of 386 cases. *Can J Ophthalmol*. 1971;6:178-182.
6. Jain IS, Pillai P, Gangwar DN, Dhir SP, Kaul VK. Congenital cataract: etiology and morphology. *J Pediatr Ophthalmol Strabismus*. 1983;20:238-242.
7. Francois J. Late results of congenital cataract surgery. *Ophthalmology*. 1979;86:1586-1598.
8. Jain IS, Pillai P, Gangwar DN, Gopal L, Dhir SP. Congenital cataract: management and results. *J Pediatr Ophthalmol Strabismus*. 1983;20(6):243-246.
9. Pratt-Johnson JA, Tillson G. Visual results after removal of congenital cataracts before the age of one year. *Can J Ophthalmol*. 1981;16:19-21.
10. Rogers GL, Tishler CL, Tsou BH, Hertle RW, Fellows RR. Visual acuities in infants with congenital cataracts operated on prior to six months of age. *Arch Ophthalmol*. 1981;99:999-1003.
11. Jan JE, Robinson GC, Scott E, Kinnis C. Hypotonia in the blind child. *Dev Med Child Neurol*. 1975;17:35-40.
12. O'Connor L. Evaluation and psychological testing. In: Jan JE, Freeman RD, Scott EP, eds. *Visual Impairment in Children and Adolescents*. New York, NY: Grune & Stratton; 1977:53-70.
13. Gelbart SS, Hoyt CS, Jastrebski G, Marg E. Long-term visual results in bilateral congenital cataracts. *Am J Ophthalmol*. 1982;93:615-621.
14. Tingle AJ, Chantler JK, Kettyls GD, Larke RPB, Schulzer M. Failed rubella immunization in adults: association with immunologic and virological abnormalities. *J Infect Dis*. 1985;151:330-336.
15. Current trends: rubella and congenital rubella syndrome—United States, 1984-1985. *MMWR*. 1986;35:129-134.
16. Guy LP. Postnatal cataracts in premature infants. *Am J Ophthalmol*. 1954;38:65-68.
17. Liebman SD. Postnatal development of lamellar cataracts in premature infants. *Arch Ophthalmol*. 1955;54:257-258.
18. Brown CA. Post-natal cataracts in premature infants. *Eye*. 1963;83:493-504.
19. Gabilan JC, Chaussain JL. L'Association hypoglycemie idiopathique et cataracte chez l'enfant. *Arch Fr Pediatr*. 1969;26:633-640.
20. McKinna AJ. Neonatal hypoglycemia: some ophthalmic observations. *Can J Ophthalmol*. 1966;1:56-59.
21. Merin S, Crawford JS. Hypoglycemia in infantile cataract. *Arch Ophthalmol*. 1971;86:495-498.
22. Kugelberg I. Spasmophilie und Katarakt. *Acta Ophthalmol*. 1936;14:220-231.
23. Nelson LB. Diagnosis and management of cataracts in infancy and childhood. *Ophthalmic Surg*. 1984;15:688-697.
24. Jay B. Cataracts in early childhood: etiology and genetic aspects. *Proc R Soc Med*. 1976;69:268-269.

Journal Cancellations

The high cost of journal subscriptions has resulted in cancellations of journals at an enormous magnitude throughout the world. Jones and Bowden (*Science*, 1988;242:1361) report that of 13 libraries reporting in Texas, Arkansas, Louisiana, Oklahoma, and New Mexico, 1111 titles were scheduled for cancellation in 1989 and that 1955 titles were cancelled for 1988. In the same time periods, 1256 subscriptions were to be cancelled in 1989 and 2381 had been cancelled in 1988.

A Survey of Severe Eye Injuries in Children

Patrick A. DeRespinis, MD; Anthony R. Caputo, MD; Philip M. Fiore, MD; Rudolph S. Wagner, MD

• We reviewed the medical records of 258 children from newborn to 20 years of age who had ocular injuries severe enough to warrant admission to United Hospitals Medical Center, Newark, NJ, over a 3½-year period. In this time there were 1737 pediatric admissions for eye treatment and of these, 258 (14.85%) were directly related to trauma. Only strabismus, with 676 (38.9%) admissions, accounted for more pediatric hospitalizations for eye injuries. Balls, fists, and sticks were the most common causes of injury, and the most common diagnosis was hyphema. The majority of injuries occurred in children between 11 and 15 years of age (31%). Ocular injuries in children above 10 years of age were most commonly sports-related, whereas injuries in the home accounted for the majority of trauma in children younger than 10 years of age.

(*AJDC*. 1989;143:711-716)

Ocular injury is an important cause of visual loss in the pediatric population. An estimated 160 000 school-age children in the United States suffer trauma to the eye of varying severity each year.[1] In the present study, trauma was the second most frequent cause of pediatric admissions for ocular treatment, surpassed only by strabismus. Trauma is the leading cause of admission for pediatric ocular treatment of greater than 48 hours' duration, if we consider that the majority of procedures for the correction of strabismus are now performed on an ambulatory basis. In the present study we excluded admissions for ambulatory surgery and concentrated on those cases requiring more extended management.

Accepted for publication January 17, 1989.

From the Manhattan Eye, Ear & Throat Hospital, New York, NY (Dr DeRespinis); and the University of Medicine & Dentistry of New Jersey, Newark (Drs Caputo, Fiore, and Wagner).

Presented at the American Association of Pediatric Ophthalmology and Strabismus Annual Meeting, Boston, Mass, May 18-21, 1988.

Reprint requests to Eye Institute of New Jersey, 15 S Ninth St, Newark, NJ 07107 (Dr DeRespinis).

General reviews of ocular trauma are surprisingly infrequent, with the majority of publications emanating from Europe.[2-7] This may represent difficulties in amassing data relating to ocular injury and the events surrounding the initial event. In the United States the majority of medical facilities use a coding system in which admissions are catalogued according to diagnosis.[8] Unfortunately, it cannot always be ascertained from these codes if admissions were directly related to trauma. This makes data retrieval at a later date very difficult.

We undertook a retrospective study of 258 consecutive pediatric admissions for treatment of ocular trauma over a 3½-year period to understand better the causes and circumstances surrounding eye injuries in young patients.

SUBJECTS AND METHODS

We reviewed the medical records of all pediatric patients admitted to United Hospitals Medical Center of New Jersey, Newark, for ocular complaints during the past 8 years. Availability of medical records during a consecutive time period was a factor in the selection of the study dates. We eventually selected a 42-month period within the past 8 years for our study. Those patients who were in the pediatric age group (0 to 20 years old) and who were admitted because of trauma were catalogued. The following pertinent facts were recorded for each patient when available: age, sex, race, date, circumstances surrounding the injury, cause, eye involvement, and primary admitting diagnoses. A table was then assembled that listed cause and corresponding diagnosis. Age groups were divided into 5-year intervals up to 20 years of age. Causes and primary admitting diagnoses were listed according to these 5-year interval subgroups. Monthly admissions were also tabulated to determine seasonal variations. Hyphemas were graded as either +1 (0% to 30% blood in the anterior chamber), +2 (30% to 60%), or +3 (>60% blood). Eyeball lacerations were classified as either corneal, corneoscleral, or scleral.

RESULTS

United Hospitals Medical Center of New Jersey is a complex composed of four integrated institutions that include the Newark Eye and Ear Infirmary and the Children's Hospital of New Jersey. It is the eye trauma center of New Jersey and trauma cases involving the eyes are referred from a wide population area. There were 1737 pediatric admissions to the United Hospitals Medical Center of New Jersey for ocular complaints in the 3½-year study period, of which 258 (14.9%) were for trauma. The most common admitting diagnosis in this age group was strabismus, which accounted for 676 (38.9%) cases. Congenital cataracts or eye anomalies requiring examinations under anesthesia accounted for 218 (12.5%) cases. Trauma was the second leading cause of admission for ocular treatment (Fig 1).

Certain causes account for the majority of particular diagnosis (Table 1). Most eyeball lacerations were caused by glass fragments, while falls and animal bites were responsible for most adnexal lacerations. Fractures, most of which involved the orbital floor, were mostly caused by fists. Injuries from balls accounted for almost one half of the retinal detachments.

Causes were varied but sports accidents (usually involving balls), sticks, fists, and fingers accounted for most of the ocular trauma. Certain causes found preponderance in certain age groups (Table 2). For instance, 74.1% of injuries by balls, 75% of injuries by fists, and 93% of injuries by metallic foreign bodies occurred in children between the ages of 11 and 20 years. Falls (83.3%) characteristically occurred in children under 10 years of age, whereas the majority of animal bites (63.6%) occurred in the 0- to 5-year-old age group. Certain diagnoses were also more common in different age groups (Table 3). All of

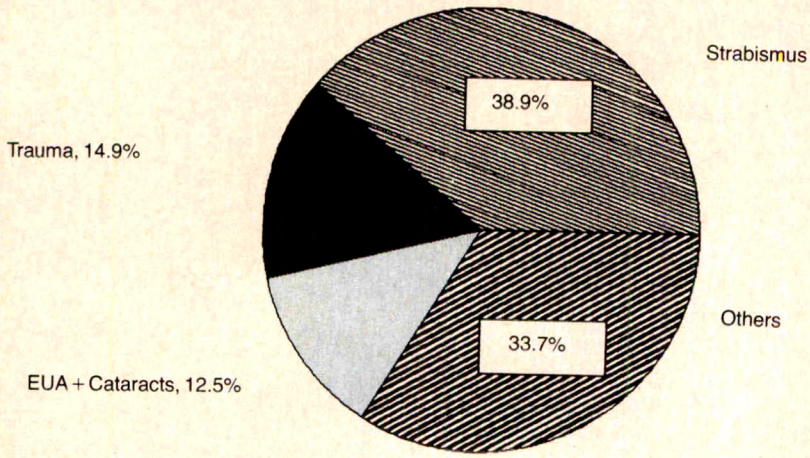


Fig 1.—Most common causes of pediatric admissions for ocular complaints (ages 0 to 20 years). Others includes ocular and orbital infections, nasolacrimal duct probes, congenital glaucoma procedures, and other admitting diagnoses. EUA indicates examination under anesthesia.

the orbital fractures and 89% of the retinal detachments occurred in children over 10 years of age. Seventy-nine percent of all lid lacerations befell children younger than 10 years of age.

Approximately 75% of the medical records we reviewed had complete documentation of the events surrounding the injury. It was found that 76.2% involved another person. Of these, 23% were violent acts such as muggings or fights. There were eight documented cases of child abuse. These injuries ranged from mere periorbital contusions to hyphemas. Fists, fingers, and belts were among the causes involved.

Boys accounted for 78.3% of the ocular injuries. The majority of traumas (31%) occurred in children 11 to 15 years of age. Children 5 years of age and younger incurred the least amount of eye trauma (19.8%) (Tables 2 and 3). The eye injuries were monocular in 98% of cases. Fifty-one percent involved the right eye and 47% involved the left eye. Four cases involved both eyes. In the present study 63.2% of patients admit-

Table 1.—Most Common Admitting Diagnoses and Their Causes

		Diagnosis, No. of Cases						
Cause	Total	Hyphema	Globe Laceration	Traumatic Cataract	Eyelid Laceration	Retinal Detachment	Foreign Body in Eye*	Orbital Fracture
Balls	**23**	9	3	2	0	9	0	0
Sticks	**22**	11	4	5	0	0	2	0
Fists, fingers	**21**	11	0	0	1	2	1	6
Falls	**17**	3	4	1	9	0	0	0
Rocks, stones	**16**	5	5	2	1	2	1	0
Metal foreign bodies	**13**	0	1	1	0	1	10	0
Glass	**12**	0	10	2	0	0	0	0
Animal bites	**10**	1	0	0	8	1	0	0
Projectiles (nonspecific)	**7**	6	0	1	0	0	0	0
Assorted toys	**7**	4	2	1	0	0	0	0
Guns, BBs	**7**	1	3	0	0	0	3	0
Hangers	**6**	2	1	1	2	0	0	0
Belts, buckles	**6**	5	1	0	0	0	0	0
Fireworks	**5**	2	0	3	0	0	0	0
Auto accidents	**5**	0	1	2	1	1	0	0
Kicking	**4**	1	0	0	2	0	0	1
Knives, scissors	**4**	0	1	2	0	1	0	0
Miscellaneous (<2 cases)	**24**	10	7	2	2	1	0	2
Unknown	**26**	10	5	6	2	1	1	1
Total	**235**	**81**	**48**	**31**	**28**	**19**	**18**	**10**

*Includes 8 of 18 extraocular foreign bodies and 8 of 18 intraocular foreign bodies with 2 of 18 nonspecific cases.

ted were black, 30.6% were white, and other racial groups made up the remainder of the study population. These percentages were consistent with the population served.

Seasonal variations in the number of admissions for pediatric ocular trauma were examined from January to December over a 3-year period (Fig 2). The greatest number of admissions for trauma, 64%, was observed in the 6-month period between May and October. The highest monthly percentage occurred in August (15.2%), and the lowest occurred in February (2.6%).

The most common primary admitting diagnosis was hyphema, of which there were 81 cases (31.4%; Fig 3). Most of cases were caused by sticks or fists and fingers. The severity of hyphema in most patients was grade 1. Because of the high occurrence rate, visual prognosis at the 3-month follow-up examination was studied. As may be expected, the best prognosis was found in patients with +1 severity and the worst was in patients with +3 severity (Table 4). After discharge, 27% of the patients with hyphema failed to return for follow-up examinations and visual acuity could not be recorded.

Eyeball laceration was the second most frequent diagnosis leading to admission (18.6%). Its occurrence was distributed fairly evenly over the four age groups except for the 6- to 10-year-old group, in which only seven cases (15%) were reported. Among globe lacerations in patients with complete medical records, 33% were purely corneal, 31% involved only the sclera, and 36% were combined corneoscleral lacerations. When the cornea was involved the recorded visual acuity at follow-up examination was less than 20/100 in approximately 75% of the cases and one third of these patients developed traumatic cataracts. The prognosis for corneal lacerations is directly related to the extent and depth of the injury. The sclera encircles the choroid, retina, ciliary body, and other vital structures in the eye. As a result, enucleation was the eventual outcome in 20% of scleral injuries.

Other diagnoses frequently seen on admission can be found in Tables 1 and 3. Eyelid lacerations occurred most commonly in patients less than 10 years of age and were most frequently caused by falls (32%) or animal bites (28.5%). Other common admitting diagnoses included traumatic cataracts, retinal detachments, ocular foreign bodies, and orbital fractures. Of note is the fact that a number of patients were admitted with more than one diagnosis. In these situations they were catalogued according to the primary admitting diagnosis.

Table 2.—Cause and Age Distributions of Ocular Trauma

Cause	Total	Age Group, No. (%) of Cases 0-5 y	6-10 y	11-15 y	16-20 y
Balls	27 (10.5)	1 (3.7)	6 (22.2)	11 (40.8)	9 (33.3)
Fist, fingers	24 (9.3)	2 (8.3)	4 (16.7)	9 (37.5)	9 (37.5)
Sticks	23 (8.9)	3 (13)	6 (26.1)	9 (39.1)	5 (21.8)
Falls	18 (7.0)	7 (38.9)	8 (44.4)	1 (5.6)	2 (11.1)
Rocks, stones	18 (7.0)	4 (22.3)	6 (33.3)	6 (33.3)	2 (11.1)
Metal foreign bodies	15 (5.8)	1 (6.6)	0 (0)	7 (46.7)	7 (46.7)
Glass	13 (5.0)	4 (30.8)	2 (15.4)	3 (23)	4 (30.8)
Animal bites	11 (4.3)	7 (63.6)	1 (9.1)	2 (18.2)	1 (9.1)
Projectiles	8 (3.1)	2 (25)	2 (25)	3 (37.5)	1 (12.5)
Guns, BBs	8 (3.1)	0 (0)	1 (12.5)	5 (62.5)	2 (25)
Assorted toys	7 (2.7)	1 (14.3)	2 (28.6)	3 (42.8)	1 (14.3)
Hangers	6 (2.3)	3 (50)	1 (16.7)	1 (16.7)	1 (16.7)
Belts, buckles	6 (2.3)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)
Fireworks	6 (2.3)	0 (0)	2 (33.3)	0 (0)	4 (66.7)
Auto accidents	5 (1.9)	1 (20)	2 (40)	1 (20)	1 (20)
Kicking	5 (1.9)	1 (20)	0 (0)	2 (40)	2 (40)
Knives, scissors	4 (1.6)	2 (50)	0 (0)	0 (0)	2 (50)
Chemicals	3 (1.2)	1 (33.3)	0 (0)	1 (33.3)	1 (33.3)
Miscellaneous (<2 cases each)	25 (9.7)	5 (20)	9 (36)	7 (28)	4 (16)
Unknown	26 (10.1)	5 (19.2)	5 (19.2)	7 (26.9)	9 (34.7)
Total (%)	**258 (100)**	**51 (19.8)**	**59 (22.8)**	**80 (31)**	**68 (26.4)**

Table 3.—Primary Diagnoses According to Age

Diagnosis	Total (%)	Age Group, No. of Cases 0-5 y	6-10 y	11-15 y	16-20 y
Hyphema	81 (31.4)	11	23	30	17
Globe lacerations	48 (18.6)	15	7	12	14
Traumatic cataract	31 (12)	5	10	5	11
Eyelid laceration	28 (10.9)	12	10	3	3
Retinal detachment	19 (7.4)	0	2	9	8
Foreign body in eye	18 (7)	2	3	7	6
Orbital fractures	10 (3.9)	0	0	7	3
Injury to orbital tissue	7 (2.7)	2	0	4	1
Burns	4 (1.6)	2	0	1	1
Vitreous hemorrhage	4 (1.6)	1	0	1	2
Traumatic glaucoma	3 (1.2)	1	1	1	0
Corneal abrasion	2 (<1)	0	2	0	0
Lens subluxation	2 (<1)	0	1	0	1
Conjunctival laceration	1 (<1)	0	0	0	1
Total (%)	**258 (100)**	**51 (19.8)**	**59 (22.8)**	**80 (31.0)**	**68 (26.4)**

COMMENT

Ocular trauma is a major cause of reduced vision and accounts for a large proportion of extended admissions for

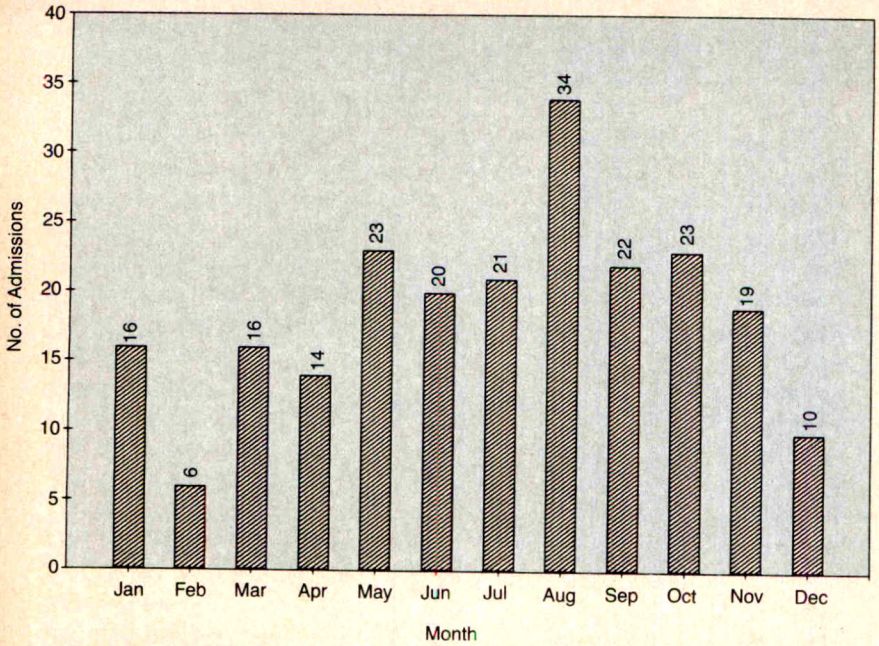


Fig 2.—Monthly variations of pediatric admissions for ocular trauma (ages 0 to 20 years). RD indicates retinal detachment.

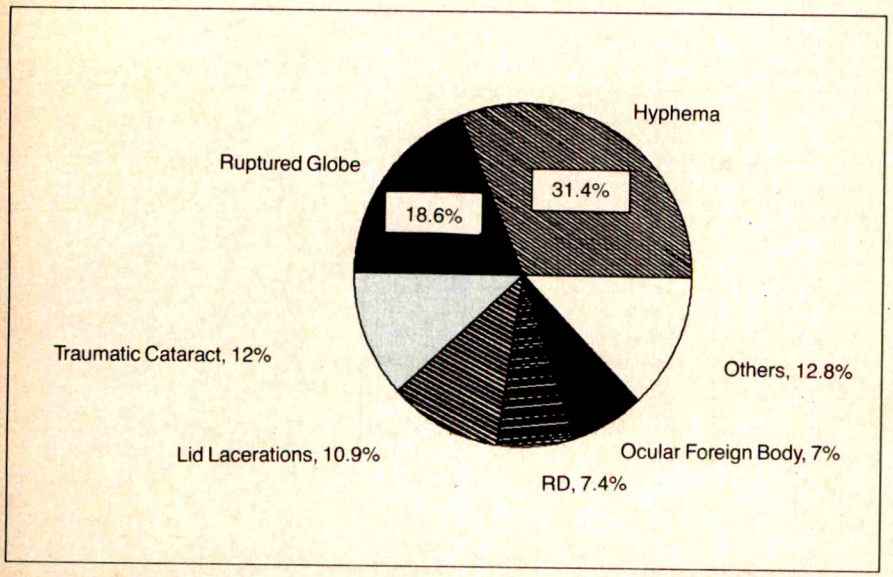


Fig 3.—Primary admitting diagnoses of pediatric patients with ocular trauma (ages 0 to 20 years). Others includes those less-frequent diagnoses listed in Table 3. RD indicates retinal detachments.

ophthalmic treatment in hospitals worldwide. One US study reported a 7.5% incidence of ocular trauma among all age groups admitted to a hospital between 1969 and 1972.[9] There was a 7.8% incidence of ocular trauma among all new admissions for ocular treatment in 1967 to a university hospital in Japan,[10] and a 12% incidence among all admissions in a Swedish hospital in 1966.[3] The rate that we found in the pediatric population (14.9%) is higher than that found in the general population. In a report by the Massachusetts Statewide Childhood Injury Prevention Program in the fall of 1984, it was estimated that each year 1 of 119 children will sustain some kind of eye injury that requires hospital treatment.[11,12] A higher percentage of admissions for ocular trauma in the pediatric age group may just reflect a lower total number of admissions for general ocular treatment in the young.

We found most pediatric ocular trauma to occur in boys, with a 4:1 predominance. This ratio corresponds closely to other studies in the young.[4-6,9,11] The frequency of ocular injuries was found to have a higher distribution in the 11- to 20-year-old age group (57.4%) and corresponded to results of a study performed in Northern Ireland over a 10-year period.[2]

There are many causes of eye trauma and it is difficult to categorize them. Older children (ages 11 to 20 years) sustained more injuries from balls, sticks, fists, and metallic foreign bodies. This may be explained by increased participation in outdoor activities without the stricter adult supervision that might be expected in a younger child. The National Society for the Prevention of Blindness, New York, NY, has estimated that three of four eye injuries occur among unsupervised children.[1] In

Table 4.—Three-Month Follow-up of Visual Acuity After Hyphema

		Visual Acuity, No. of Cases				
Degree of Hyphema	**Total**	**20/30**	**20/30-20/50**	**20/60-20/100**	**<20/100**	**Unknown**
+1	58	27	8	7	3	13
+2	7	2	2	1	1	1
+3	12	3	1	0	4	4
Unknown	4	0	0	0	0	4
Total	**81**	**32**	**11**	**8**	**8**	**22**

reviewing our data we found that the older children were especially prone to sports-related injuries. The younger children (ages 0 to 10 years) are injured more often from accidental falls in the home, usually against furniture or other household objects. These injuries might be prevented if parents were made aware of the disastrous potential of such things as a sharp-edged tabletop at a child's eye level, or eye-level display hooks at supermarket checkout counters. Furniture edge and corner guards made of rubber are available in most hardware stores and supermarkets and should be purchased by parents of young children.

Although 76% of the ocular trauma in our series involved another individual, less than one fourth of the injuries were due to violent acts. Most injuries occurred during sports, recreation, or casual play. In 1981, Niiranen and Raivio[4] found approximately one half of all eye injuries to be caused by another child, and a study by the National Society for the Prevention of Blindness estimated that two thirds of all pediatric eye injuries occur during play and sports participation.[1] Protective eyewear is commercially available to the general public in the form of one-piece eye guards constructed of impact-resistant polycarbonate lenses. The patient's own prescription lens can be placed in this style of protective eyewear. These guards should be worn especially during high-velocity games played in enclosed courts (eg, racquetball or squash). Parents and physicians are aware of the damage that can be caused by a well-hit tennis or racquet ball, but any toy store contains dozens of potentially dangerous toy weapons and projectiles that are readily available to the uneducated consumer. The injuries or loss of vision caused by these products can be prevented if the items are simply not purchased by the parent.

The preponderance of ocular trauma in our study was found to occur between the months of May and October. In a 10-year study of eye injuries in Northern Ireland, 55.3% of admissions related to ocular trauma occurred from May to October, with the largest percentage of injuries occurring in August and the lowest percentage occuring in January and February.[2] Grin et al[13] in 1987 found the largest number of accidents to occur between April and June (33.8%) and the smallest number to occur between January and March (18.4%). These results are very similar to ours and emphasize the fact that warm weather provides a greater opportunity for ocular injury. It is during these months that more sporting activities and outdoor play take place. There is a lack of adult supervision because school is not in session. Also, the lengthened day in the warmer months increases the child's chance of being exposed to situations that may cause ocular injury.

In our series, hyphema was the leading cause of admission. Most practitioners still feel that children with hyphema should be admitted to a hospital for treatment and close observation for a period of 5 days. A Nigerian study[14] noted that 75% of admissions for hyphema occurred in patients under 20 years of age. The prevalence of hyphema has been found to be as high as 66% of the total admitting diagnoses[4] among children in comparative studies. Whether this is because a child's eye is more susceptible to this type of injury or because children with hyphema are admitted more often than adults is beyond the scope of the present report.

In our study the instruments that most commonly caused hyphema were sticks or fists and fingers (both in 11 cases [13.5%]). A study by Edwards and Layden[15] found rocks (24%) and missiles (22%) to be the major cause of hyphema. Their study found fists and sticks to be responsible for 10% and 12% of the cases, respectively, in close agreement with our findings. Almost all young children are infatuated with sticks and branches found in yards, and adults should instruct their children in the dangers of these objects.

As may be expected, better visual acuity corresponded with less severe grades of hyphema. Previous studies have shown this same clinical correlation.[9,14,15] It should be evident that a greater hyphema carries a graver visual prognosis and is indicative of more serious complications.

Ruptured globes were present in 18.6% of the cases in our study. Perforating eye injuries accounted for 5% of all admissions for ocular treatment at 12 European eye clinics in the 1950s and 1960s.[16] Depending on the study, there appeared to be a wide range (8.9%[4] to 65.5%[5] of the total hospitalizations for eye trauma) in the incidence of ruptured globes leading to admission. Scleral involvement led to a greater incidence of eventual enucleation (20%). Cinotti and Maltzman[17] found this clinical correlation to be 33%. In any case, scleral involvement carries a graver prognosis than an uncomplicated corneal laceration. The recent literature indicates that the incidence of globe lacerations has apparently become a less frequent cause of admission. This decreased incidence of eyeball lacerations may be due to changes in consumer safety standards and heightened awareness of the causative factors. Our literature survey shows that we still have a long way to go toward preventing the needless loss of sight due to lacerations of the globe.

The main source of foreign bodies in the eyes was metallic fragments that were usually propelled into the eye by hammering or drilling or grinding with high-speed tools while in shop class or at home pursuing hobbies. In 8 of 18 patients the foreign bodies were found lodged extraocularly, usually in the cornea. The remainder were found intraocularly. This emphasizes the need for the use of protective eyewear even in the pediatric population.

Many authors have pointed out in their series that difficulties were encountered performing retrospective studies because of the improper information-collecting techniques inherent in admissions for trauma. Poor note-taking and misplaced follow-up visit information appeared to be the rule and not the exception. We propose that a trauma admission sheet be used to improve the care and follow-up of our patients admitted for ocular trauma. This document would become a permanent part of the patient's medical record. It would address all of the pertinent facts surrounding the nature and circumstances of the injury. It would be retrievable when the patient returned for follow-up examination, and at that time the appropriate information concerning the patient's progress would be included. In this way we might better understand and minimize the problem of data retrieval pertaining to admission for ocular trauma.

Trauma continues to be a major cause of reduced vision and of admission for ocular treatment, especially among pediatric patients. Physicians, parents, teachers, and those responsible for the care of the young should be aware of the causative factors involved in ocular trauma and the potential dangers found in seemingly benign objects. Children should be instructed in proper prevention and protective eyewear should be worn when appropriate. The real treatment of serious ocular injuries does not lie in medical therapy or surgical technique, but in prevention.

This study was supported in part by the Gershowitz Grant at the Pediatric Ocular and Learning Center, Manhattan Eye, Ear & Throat Hospital, New York, NY (Dr DeRespinis), and Fight For Sight Inc, New York.

References

1. *National Society for the Prevention of Blindness, Data Analysis: Vision Problems in the US.* New York, NY: National Society for the Prevention of Blindness; 1978:24-33.
2. Canavan YM, O'Flaherty MJ, Archer DB, Elwood J. A ten year survey of eye injuries in Northern Ireland, 1967-1976. *Br J Ophthalmol.* 1980;64:618-625.
3. Lindstedt E. Causes of blindness in Sweden. *Acta Ophthalmol.* 1967;8:717-722.
4. Niiranen M, Raivio I. Eye injuries in children. *Br J Ophthalmol.* 1981;65:436-438.
5. Werner S. On injuries to the eyes of children. *Acta Ophthalmol.* 1952;30:97-104.
6. Lambah P. Some common causes of eye injuries in the young. *Lancet.* 1962;2:1351-1353.
7. Agugini G, Bizzi G. Infortuni oculari nell'infanzia: casistica del Pio Instituto Oftalmico di Milano dal 1949 al 1968. *Minerva Pediatr.* 1970;22:1647-1652.
8. *International Classification of Diseases: Clinical Modification, 9th Revision.* Ann Arbor, Mich: Edwards Bros Inc; 1986.
9. Maltzman BA, Pruzon H, Mund ML. A survey of ocular trauma. *Surv Ophthalmol.* 1976;21:285-290.
10. Yuasa T, Bessyo T, Ishibashi T, Seguchi T. Statistical observations of ocular injuries. *Folia Ophthalmol Jpn.* 1967;18:717-722.
11. Gallagher SS, Stock L, Bromberg J, Mierzwa K. Childhood and adolescent eye injuries: an overlooked problem. *SCIPP Reports.* (Boston, Mass, Statewide Childhood Injury Prevention Program, Massachusetts Department of Public Health.) Fall 1984:1-3.
12. Gallagher SS, Guyer B, Kotelchuck M, et al. A strategy for the reduction of childhood injuries in Massachusetts: SCIPP. *N Engl J Med.* 1982; 307:1015-1019.
13. Grin TR, Nelson LB, Jeffers JB. Eye Injuries in childhood. *Pediatrics.* 1987;80:13-17.
14. Amoni SS. Traumatic hyphaema in Kaduna, Nigeria. *Br J Ophthalmol.* 1981; 65: 439-444.
15. Edwards WC, Layden WE. Traumatic hyphema: a report of 184 consecutive cases. *Am J Ophthalmol.* 1973;75:110-116.
16. Niiranen M. Perforating eye injuries treated at Helsinki University Eye Hospital 1970-1977. *Ann Ophthalmol.* 1981;13:957-961.
17. Cinotti AA, Maltzman BA. Prognosis and treatment of perforating ocular injuries. *Ophthal Surg.* 1975;6:54-61.

Book Review

Books Received but Not Reviewed

Pediatric Home Care, by L. Aday, M. J. Aitken, D. H. Wegener, 464 pp, $34.95, Chicago, Ill, Pluribus Press Inc, 1988.

Pediatric Otology, Volume 40 in Advances in Oto-RhinoLaryngology, edited by C. Cremers, G. Hoogland, 176 pp, $99.50, New York, NY, S Karger AG, 1988.

Pediatric Tumors of the Genitourinary Tract, by B. H. Broecker, F. A. Klein, 346 pp, $72, New York, NY, Alan R Liss Inc, 1988.

Perinatal Medicine: Problems and Controversies, by G. DiRenzo, D. Hawkins, 237 pp, $47, New York, NY, Raven Press, 1986.

Perinatal Nutrition, by B. S. Lindblad, 418 pp, $65, Orlando, Fla, Academic Press Inc, 1988.

Perspectives in Critical Care, by F. B. Cerra, 197 pp, $145, St Louis, Mo, Quality Medical Publishing Inc, 1988.

Practical Paediatric Nutrition, by E. Poskitt, 307 pp, $49.95, Stoneham, Mass, Butterworth Publishers Inc, 1988.

Primary Medical Care of Children and Adolescents, by W. Feldman, W. Rosser, P. McGrath, 280 pp, $29.95, New York, NY, Oxford University Press, 1988.

Psychocutaneous Disease, by C. S. Koblenzer, 352 pp, $49.50, Philadelphia, Pa, WB Saunders Co, 1987.

Psychosocial Scenarios, by P. V. Trad, 285 pp, $44, New York, NY, Springer-Verlag NY Inc, 1988.

Pure Red Cell Aplasia, by E. Dessypris, 173 pp, $32.50, Baltimore, Md, The Johns Hopkins University Press, 1988.

Questions and Answers in Otolaryngology, by M. R. Hawthorne, B. J. G. Bingham, 248 pp, $15, Littleton, Mass, PSG Publishing Co Inc, 1988.

A Remarkable Medicine Has Been Overlooked, by James Dreyfus, 384 pp, $4.95, New York, NY, Dreyfus Medical Foundation, 1983.

Renal Genitourinary Disorders: Progression, Replacement Therapy, Growth: Current Concepts in Diagnosis and Management, edited by J. Strauss, 431 pp, Miami, Fla, University of Miami Press, 1988.

Retinopathy of Prematurity: Problem and Challenge, by J. T. Flynn, D. Phelps, 364 pp, $140, New York, NY, Alan R Liss Inc, 1988.

Review of Pediatrics, by R. D. Krugman, 176 pp, $24.95, Philadelphia, Pa, WB Saunders Co, 1987.

Scott-Brown's Otolaryngology, by A. G. Kerr, 586 pp, $110, Stoneham, Mass, Butterworth Publishers Inc, 1988.

The Sexual Pharmacy: The Complete Guide to Drugs With Sexual Side Effects, by M. L. Lieberman, 331 pp, $18.95, New York, New American Library, 1988.

Smith's Recognizable Patterns of Human Deformation, by J. M. Graham, 191 pp, $35, Philadelphia, Pa, WB Saunders Co, 1988.

Sudden Infant Death Syndrome: The Possible Role of the 'Fear Paralysis Reflex,' by B. Kaasa, 59 pp, $18.95, New York, NY, Oxford University Press, 1988.

The Supportive Care of the Child With Cancer, A. Oakhill, 290 pp, $45, Littleton, Mass, PSG Publishing Co Inc, 1988.

Surface Topography and Spinal Deformity, by I. Stokes, A. Pekelsky, F. Moreland, 425 pp, $97, New York, NY, VCH Publishing Co, 1988.

Technology-Dependent Children: Hospital vs Home Care: Office of Technology Assessment Task Force, 105 pp, $27.50, New York, NY, JB Lippincott Co, 1988.

Topics in Pediatric Genetic Pathology: The Enid Gilbert-Barness Festschrift, by J. M. Opir, J. Bernstein, L. M. Spano, 489 pp, $90, New York, NY, Alan R Liss Inc, 1987.

Treating Family Violence in a Pediatric Hospital: A Program of Training, Research and Services, by K. M. White, J. Snyder, R. Bourne, E. H. Newberger, 100 pp, Washington, DC, Dept of Health and Human Services, 1988.

Trends in Pharmacological Research on Platelet Activating Factor (PAF) in Japan, by Y. Ogura, 223 pp, $28, St Louis, Mo, Ishiyaku Euroamerica Inc, 1988.

Tuberculosis, by D. Schlossberg, 245 pp, $79, New York, NY, Springer-Verlag NY Inc, 1988.

Tuberculous Meningitis Tuberculomas and Spinal Tuberculosis: A Handbook for Clinicians, by M. Parsons, 137 pp, $29.95, New York, NY, Oxford University Press, 1988.

Understanding AIDS, by E. Lerner, 64 pp, $9.95, Minneapolis, Minn, Lerner Publications Co, 1988.

Using Media to Make Kids Feel Good, by M. Gaffney, 232 pp, $35, Phoenix, Ariz, Oryx Press, 1988.

When Food's a Foe: How to Confront and Conquer Eating Disorders, by N. Kolodny, 152 pp, $14.95, Boston, Mass, Little Brown & Co Inc, 1987.

The Diagnosis of Neurofibromatosis-1 in the Child Under the Age of 6 Years

Angela C. Obringer, PhD; Anna T. Meadows, MD; Elaine H. Zackai, MD

• One-hundred sixty children under the age of 6 years presented for diagnostic evaluation regarding neurofibromatosis-1 (NF-1). Using the National Institutes of Health Consensus Conference criteria, 151 (94%) of the children were classified on initial examination: 112 were diagnosed as having NF-1 and 39 were found to be unaffected (all 39 have remained asymptomatic on follow-up). Nine could not be classified (3 have subsequently met minimal diagnostic criteria on follow-up). Clinical manifestations of NF-1 include cafe au lait spots (97%), freckling in the axillary or inguinal region (81%), Lisch nodules (30%), neurofibromas (15%), pseudoarthrosis (6%), and optic nerve gliomas (4%). More than minimal diagnostic criteria were met by 80% of the children who had a positive family history and by 32% of those who did not. Thus, the clinical diagnosis of NF-1 is possible in the child who is under 6 years of age, and the National Institutes of Health criteria are useful and applicable.

(*AJDC*. 1989;143:717-719)

Neurofibromatosis is one of the most common single gene disorders, occurring in 1 in 4000 live births, with virtually complete penetrance of a dominant gene. Although linkage analysis has localized the gene for von Recklinghausen neurofibromatosis (neurofibromatosis-1 [NF-1]) to the centromeric region of chromosome 17,[1] the diagnosis of NF-1 at this time is still dependent on clinical evaluation. In young children, the diagnosis has been especially difficult because of the variation in gene expression with age. In the absence of a positive family history (which occurs in 50% of cases), the diagnosis is based solely on clinical signs.

A recent National Institutes of Health (NIH) Consensus Conference[2] defined the two forms of neurofibromatosis (NF-1 [Table 1] and NF-2) and established specific guidelines for diagnosis (NF-2, previously known as bilateral acoustic neurofibromatosis or central neurofibromatosis, includes individuals who meet at least one of the two following criteria: having a bilateral eighth nerve mass that can be seen with appropriate imaging techniques, eg, computed tomography or magnetic resonance imaging; or having a first-degree relative with NF-2 and either [1] a unilateral eighth nerve mass or [2] two of the following: neurofibroma, meningioma, glioma, schwannoma, and juvenile posterior subcapsular lenticular opacity). We reviewed the results of our examination of 160 children who were initially evaluated for NF-1 between birth and 6 years of age. The objective was to determine the applicability of these diagnostic criteria in young children and the frequency of clinical manifestations in this age group.

Accepted for publication January 12, 1989.

From the Divisions of Oncology (Drs Obringer and Meadows) and Human Genetics and Molecular Biology (Dr Zackai), The Children's Hospital of Philadelphia (Pa).

Reprint requests to Division of Human Genetics and Molecular Biology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (Dr Zackai).

PATIENTS AND METHODS

The Neurofibromatosis Clinic at The Children's Hospital of Philadelphia (Pa) was established in 1979. Pediatric patients and their families have been referred to this multidisciplinary clinic by physicians in the community, by physicians at outpatient medical clinics, and through information disseminated by the media.

By the end of 1987, 860 individuals had been examined. The diagnosis of NF-1 was made in 375. In children, the diagnosis was based on the clinical presentation, physical and neurologic examinations, and ophthalmologic and radiologic findings. All children were examined completely unclothed. The number and size of cafe au lait spots and neurofibromas were recorded. The presence or absence of axillary and inguinal freckling was noted. Head circumference, height, weight, and blood pressure were recorded. Skeletal surveys were reviewed, and an eye examination was performed by an ophthalmologist who was familiar with the ocular manifestations of NF-1. Parents and other adults who were examined were evaluated using the criteria established by Crowe et al.[3]

Using the criteria established by the 1987 NIH Consensus Conference (Table 1), we reviewed the records of all children who were initially evaluated between 1979 and 1987, and who were under 6 years of age at that evaluation (160 patients). Each child was categorized according to mode of inheritance, age at examination, and clinical manifestations. The population was divided into two categories: (1) those with one parent affected and thus needing only one other criterion (criteria 1 through 6) for diagnosis (familial); and (2) those with neither parent affected (sporadic) and those with unknown parental status (only one parent examined and unaffected or the child was adopted), and thus needing to meet at least two of the criteria (criteria 1 through 6) for diagnosis.

The findings at follow-up examinations of all patients were reviewed. Follow-up examinations are performed annually on all affected individuals; all unaffected siblings in familial cases are seen annually until the age of 6 years. History regarding the health of the unaffected siblings is taken thereafter at the annual visit of the affected sibling.

RESULTS

Of the 160 children under 6 years of age at initial evaluation, 151 (94%) were classified using the criteria established by the NIH Consensus Conference (Table 2). There were 112 children classified as having NF-1; and 39, as unaffected. Nine patients could not be classified.

Family History and Age at Initial Evaluation

Seventy-five of the children had an affected parent; however, physical examination of both parents of 73 of the children showed no signs of NF-1. In 12

Table 1.—Criteria for Diagnosis of Neurofibromatosis-1 (NF-1) (von Recklinghausen Neurofibromatosis)

The diagnostic criteria for NF-1 are met in an individual with two or more of the following criteria:

1. Six or more cafe au lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in postpubertal individuals
2. Two or more neurofibromas of any type, or one plexiform neurofibroma
3. Freckling in the axillary or inguinal region
4. Optic glioma
5. Two or more Lisch nodules
6. A distinctive osseous lesion, eg, sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. A first-degree relative (parent, sibling, or offspring) with NF-1 according to the above criteria

cases, only one parent was available for examination and no abnormalities were found, or the child was adopted and, therefore, the family history could not be determined (Table 2).

All of the 75 children with a positive family history were classified. Fifty-five were affected, and 20 were unaffected. There were 47 children under 3 years of age. Of these, 37 had a diagnosis of NF-1. In the remaining 10, there were no clinical signs of NF-1. Twenty-eight children were initially evaluated between the ages of 3 and 6 years. Eighteen were classified as affected, and 10 were unaffected (Table 3). The 20 unaffected children have remained without clinical signs on follow-up examination; 11 are between 6 and 11 years of age.

Seventy-three of the children had a negative family history. Of the 73, 49 were classified as affected, 15 were unaffected, and 9 could not be classified. Thirty-eight were initially seen between the ages of 0 and 3 years, with a positive diagnosis in 26. In 6, the diagnosis of NF-1 could not be made. One of these patients was considered to be unaffected in a follow-up examination at the age of 4½ years. Of the 3- to 6-year-old children, 23 were classified as having NF-1, 9 were unaffected, and the diagnosis was undetermined in 3 (Table 3). One of the 3 children was followed up until he was 7½ years old, at which time he was considered to be unaffected. Of the 7 remaining patients in this group who could not be classified, 2 have been unavailable for follow-up and the other 5 (age range, 4½ to 12 years) do not yet meet the criteria for NF-1.

All of the 12 children with undetermined family history were classified. Eight were under 3 years of age at initial examination. Four were affected and 4 were unaffected. The 4 children who were seen when they were between 3 and 6 years of age met the clinical criteria for the diagnosis of NF-1.

Several individuals referred to the Neurofibromatosis Clinic without a positive family history and considered to be unaffected by the NIH Consensus Conference criteria often had other diagnoses that involved hyperpigmentation. These included urticaria pigmentosum, Becker's nevus, and piebaldism. Two children presented with plexiform neurofibromas of the orbit and absence or dysplasia of the sphenoid wing. Neither had any cafe au lait spots, axillary freckling, or other neurofibromas. One was 6 months old at the initial examination, and one was 5½ years at the initial visit. Follow-up examinations over periods of 3 and 6 years, respectively, have shown that neither patient has developed any other positive clinical signs. Another child had cafe au lait spots and axillary freckling only on the upper right quadrant of the body. The remaining patients who were categorized as having another disorder usually presented with two to three cafe au lait spots, mild developmental delay, or failure to thrive. Follow-up by private physicians and/or the Neurofibromatosis Clinic has not led to a change in the classification of these individuals.

Table 2.—Diagnosis of Neurofibromatosis-1 in Children Under 6 Years of Age

	Diagnosis		
Family History	**Affected**	**Unaffected**	**Undetermined**
Positive (75)	55	20	...
Negative (73)	49	15	9
Undetermined (12)	8	4	...
Total (160)	**112**	**39**	**9**

Table 3.—Age at Initial Presentation

	0 to 3 y			3 to 6 y		
Family History	**Affected**	**Unaffected**	**Unknown**	**Affected**	**Unaffected**	**Unknown**
Positive (75)	37	10	...	18	10	...
Negative (73)	26	6	6	23	9	3
Undetermined (12)	4	4	...	4	...	...
Total	**67**	**20**	**6**	**45**	**19**	**3**

Table 4.—Clinical Diagnostic Criteria of Initial Evaluation by Age (N = 122)

	0 to 3 y	3 to 6 y	Total, No. (%)
Cafe au lait spots, cm	65	44	**109** (97)
0.5-1.5	27	8	**35** (29)
>1.5	38	36	**74** (68)
Axillary/inguinal freckling	54	37	**91** (81)
Lisch nodules	17	17	**34** (28)
Neurofibromas	5	12	**17** (15)
Osseous lesions	5	2	**7** (6)
Optic glioma	4	1	**5** (4)

Clinical Manifestations

The most common clinical manifestation seen in the 122 children with NF-1 was cafe au lait spots (Table 4). One hundred nine children (97%) had six cafe au lait spots that were greater than 0.5 cm in diameter. In fact, 68% had six or more cafe-au-lait spots that were greater than 1.5 cm in diameter (the postpubertal criterion). The 3 patients who had less than six cafe au lait spots had a positive family history and another clinical criterion, axillary freckling, for classification. Axillary and/or inguinal freckling occurred in 81%; Lisch nodules, in only 30%; neurofibromas, in 15%; pseudoarthrosis or tibial bowing, in 6%; and optic gliomas, in 4%.

Forty-four (80%) of the 55 children with a positive family history, in whom only one other criterion was necessary for the diagnosis of NF-1, had two or more positive clinical signs. Of the 37 children under 3 years of age, only 9 had one criterion, 18 had two criteria, and 10 had three criteria. Of the 18 patients who were between 3 and 6 years of age, only 2 had a single diagnostic criterion, 4 had two criteria, and 12 had three criteria (Table 5).

The sporadic cases and those in which the family history was unknown re-

Table 5.—Number of Positive Clinical Signs*

Family History	Positive Clinical Signs 1	2	3	4
Positive (55)	11	22	20	2
Negative (49)	NA	32	13	4
Undetermined (8)	NA	7	1	. . .
Total (112), No. (%)	**11** (10)	**61** (54)	**34** (30)	**6** (5)

*NA indicates not applicable.

Table 6.—Clinical Diagnosis in Patients Under 1 Year of Age

Family History	Affected	Unaffected	Unknown
Positive (19)	13	6	0
Negative (12)	7	3	2
Undetermined (4)	2	2	0
Total (35)	**22**	**11**	**2**

quired two or more criteria for the diagnosis of NF-1. Eighteen (32%) of 57 children had more than two positive criteria. In the 0- to 3-year-old group (N = 30), 24 had two criteria and 6 had three criteria. There were 27 patients over the age of 3 years: 15 had two criteria; 8 had three criteria, and 4 had four criteria for the diagnosis of NF-1.

Diagnosis in the Infant Under 1 Year of Age

There were 35 children under 1 year of age at initial presentation. Using the diagnostic criteria, it was possible to classify 33 of them. There were 22 affected and 11 unaffected. In 2, the diagnosis could not be determined (Table 6). The most common clinical manifestation was cafe au lait spots. In fact, two thirds (14 patients) had six cafe au lait spots that were greater than 1.5 cm in diameter. Axillary freckling was the next most common finding (18 patients). Four patients had Lisch nodules, 2 had pseudoarthrosis or tibial bowing, and 1 had multiple neurofibromas.

Neoplasms in the Child Under 6 Years of Age

At the time of evaluation, eight children had previously been diagnosed as having neoplasia as follows: Wilms' tumor (one 6-month-old patient), embryonal rhabdomyosarcoma (two patients: 1 and 3 years old, respectively), and juvenile chronic myelogenous leukemia (five patients: aged 1½ years, 2 years 4 months, 2½ years, 2 years 11 months, and 3 years 2 months, respectively). Two of these patients have developed a second primary neoplasm. The patient with Wilms' tumor developed acute lymphocytic leukemia at 6 years of age. A patient with an orbital rhabdomyosarcoma developed a brain-stem glioma in the field of previous radiation therapy. Three other children have developed neoplasms since their initial visit: two, optic nerve gliomas; and one, brain-stem glioma.

COMMENT

The clinical spectrum of NF-1 has been well-documented,[3,4] but few authors have specifically dealt with the presentation of NF-1 in young children. This retrospective review of the initial visit of 160 children under 6 years of age who were seen at the Neurofibromatosis Clinic has shown that it was possible to determine definitive classification in 151 (94%) of them using the NIH definition for diagnosis of NF-1. There were 112 children with NF-1 and 39 who were unaffected. Only 9 could not be classified at initial examination. The NIH Consensus Conference criteria are useful when considering the clinical diagnosis of NF-1 in young children.

The diagnosis of NF-1 was established in 89 of 112 of the children by cafe au lait spots and axillary freckling alone. Of those children with a positive family history, in whom only one clinical criterion was necessary for diagnosis, 80% had two or more positive clinical signs (the majority being cafe au lait spots and axillary freckling). Certain clinical features, such as neurofibromas and Lisch nodules, often do not become manifest until adolescence or adulthood. The low frequency of these criteria in our population support other clinical observations.[5]

Follow-up examination of these children has been valuable in documenting the progress of this disorder. Except for the children who were initially seen in 1987, 73 children with NF-1 have been seen for at least one additional visit. An increase in the number of cafe au lait spots, the appearance of axillary or inguinal freckling, and Lisch nodules were the most common findings associated with increasing age. Other problems, such as delay in language development, speech disarticulation, and learning disabilities, have been noted as the children approach school age.

Follow-up also has proved to be useful in confirming clinical impressions, particularly in those individuals in whom classification could not be determined initially. Three of the nine patients whose diagnoses were uncertain have been classified as unaffected on follow-up examination at 4 ½, 6, and 7 ½ years of age, respectively. The remaining six patients continue to be monitored.

Although the age at which NF-1 is diagnosed is not predictive of the possible serious consequences of the disorder, early diagnosis of NF-1 is important. It allows the parents to adjust to the diagnosis, before the advent of serious illness. It provides the opportunity for genetic counseling and education of the family about neurofibromatosis—awareness of the serious consequences of this disorder, appropriate medical follow-up, and early intervention. The guidelines of the NIH Consensus Conference are a very useful resource to the definitive diagnosis of NF-1, particularly in the young child.

References

1. Barker D, Wright E, Nguyen L, et al. Gene for von Recklinghausen neurofibromatosis is in the pericentric region of chromosome 17. *Science.* 1987;236:1100-1102.
2. National Institutes of Health. *Neurofibromatosis: National Institutes of Health Consensus Development Conference Statement.* Bethesda, Md: National Institutes of Health; July 1987;6.
3. Crowe FW, Schull WJ, Neel JV. *A Clinical, Pathological and Genetic Study of Multiple Neurofibromatosis.* Springfield, Ill: Charles C Thomas Publisher; 1956.
4. Riccardi VM: Von Recklinghausen neurofibromatosis. *N Engl J Med.* 1981;305:1617-1626.
5. Dunn DW. Neurofibromatosis in childhood. *Curr Probl Pediatr.* 1987;17:445-497.

Racial Differences in Young Children's Blood Pressure

Responses to Dynamic Exercise

Frank A. Treiber, PhD; Linda Musante, PhD; William B. Strong, MD; Maurice Levy, EdD

• Studies have observed that black children exhibit greater blood pressure increases in response to dynamic exercise than white children. Seventy-five (51 white, 24 black) children aged 4 to 6 years old had their blood pressure and heart rate measured before, during, and 5 minutes after dynamic upright exercise on the treadmill. Girls had higher preexercise heart rate values than the boys, and showed a marginally slower recovery of diastolic blood pressure values. Black children had significantly lower preexercise and peak exercise heart rate values, higher systolic blood pressure values at peak exercise, and greater systolic blood pressure increases in response to exercise than did white children. These differences are discussed in terms of mechanisms that may be responsible for racial differences in essential hypertension.

(*AJDC.* 1989;143:720-723)

Several studies have observed that black children exhibit greater increases in blood pressure and/or heart rate (HR) in response to physical[1,2] and psychological[3,4] stress than white children. These findings parallel those obtained in studies of adults.[5,6] They are important because exaggerated cardiovascular reactivity among black people may partially account for the well-established racial differences in the incidence of hypertension and hypertension-related morbidity and mortality.[7,8]

Most studies on this subject have tested either older children or adolescents, and little research has examined racial differences in reactivity to stress in children under the age of 7 years (for review, see Sallis et al[9]). Hence, it is unclear whether these racial differences are manifest in early childhood or only become apparent later. Identifying such differences in young children may implicate pathophysiologic mechanisms that are genetically determined or developed very early, secondary to cultural-environmental factors. The major purpose of the present study was to examine blood pressure responses to submaximal dynamic exercise in a biracial group of 4- to 6-year-old children. Based on previous research involving upright exercise, black children were predicted to show greater blood pressure increases in response to exercise than white children.

A second purpose was to examine gender differences in reactivity to submaximal exercise. Boys and girls of this age generally do not differ in resting blood pressure,[10,11] but few studies have examined childhood gender differences in cardiovascular reactivity to stress. One study found boys to exhibit larger cardiovascular responses to psychological stress,[12] but other studies of preadolescents have found no gender differences in reactivity.[13]

SUBJECTS AND METHODS

Seventy-five healthy children participated as part of a longitudinal study of life-style behaviors associated with cardiovascular health (Project SCAN—Study of Children's Activity and Nutrition). The children ranged in age from 4 to 6 years (mean ± SD, 5.4 ± 0.55 years) with the following race and gender distribution: 51 white (22 male) and 24 black (15 male). Written informed consent was obtained from a parent, and the child granted assent as approved by our institutional Human Assurance Committee.

The child was first given verbal explanations of the procedures and demonstrations of the equipment and how to run on the treadmill. To increase the likelihood of maximum voluntary effort, a mental imagery challenge task was employed. The children wore Superman/Superwoman capes and were told that their task was to help Superman/Superwoman catch the comic book/cartoon villain of their choice (Darth Vader, Skeletor, etc). A structured protocol, which is available on request, was used to provide verbal incentives and further elicitation of mental imagery during the exercise test.

After this preparation, a blood pressure cuff for use with an automated blood pressure monitor (Dinamap Monitor Model 1165, Critikon Inc, Tampa, Fla) was placed on the child's right arm. The cuffs chosen were 40% to 50% of the circumference of the upper arm of each subject, which is the size recommended for this type of monitor.[14] This monitor has been validated for use during exercise testing with children as young as 5 years of age.[15] Silver/silver chloride electrodes were attached to the chest for use with a direct writing electrocardiograph (IMC Lifeline, Siemens Co, Englewood, Colo) with a paper speed of 25 mm/s and a standard of 1 mV equal to 10 mm that was calibrated for paper speed and frequency response every third subject.

After a 5-minute rest period, a preexercise recording was made of HR and systolic and diastolic blood pressure (SBP and DBP). The child then ran for at least three continuous 1-minute work loads. The electrocardiogram (HR) was recorded throughout each minute, and SBP and DBP were measured during the last 30 seconds of each minute, beginning with the third work load. The progression of work loads was a 0% grade for the first minute at 4.0 km/h, a 2% grade at 5.6 km/h for the second minute, and from the third minute on, the grade increased each minute by 2% with a constant speed of 6.4 km/h. The child was urged to run until exhausted. Following completion of the exercise, HR, SBP, and DBP were assessed during the fifth minute of recovery.

RESULTS

Anthropometrics

Preliminary analyses showed no racial or gender differences in age,

Accepted for publication January 13, 1989.

From the Departments of Pediatrics (Drs Treiber, Strong, and Levy), Psychiatry (Dr Treiber), and Health Behavior (Dr Treiber), and the Georgia Institute for the Prevention of Human Disease and Accidents (Drs Treiber, Musante, Strong, and Levy), Medical College of Georgia, Augusta; and the Department of Psychology, University of Tampa (Fla) (Dr Musante).

Reprint requests to Department of Pediatrics, Georgia Prevention Institute, Medical College of Georgia, 1245 15th St, Building FT-100, Augusta, GA 30912-3770 (Dr Treiber).

weight, obesity (Quetelet index), or body surface area[16] ($P>.12$ for all values). The means and SDs by race are presented in Table 1.

Cardiovascular Responses to Exercise

Boys and girls showed similar levels of endurance time and HR during exercise. There were no gender differences in either endurance time (boys, 5.4 ± 1.7 minutes; girls, 5.0 ± 1.9 minutes; $P>.30$) or peak HR achieved during exercise (boys, 177 ± 15.3 beats per minute; girls, 181 ± 12.0 beats per minute; $P>.23$). There were no racial differences in endurance time (white children, 5.2 ± 1.9 minutes; black children, 5.0 ± 1.4 minute; $P>.56$). However, white children reached significantly higher peak HR values during exercise (white children, 182 ± 13.6 beats per minute; black children, 173 ± 12.3 beats per minute; $P<.008$).

To assess racial and gender differences in preexercise, peak exercise, and recovery HR, SBP, and DBP values, a series of ANOVAs was conducted. Girls had higher preexercise HR than males (boys, 99.4 ± 14.0 beats per minute; girls, 105.9 ± 13.6 beats per minute; $P<.04$) No other significant gender effects on absolute values of preexercise, peak exercise, and recovery HR, SBP, or DBP were obtained (all $P>.12$).

Table 2 presents means and SDs of absolute HR, SBP, and DBP values at preexercise, peak exercise, and recovery for black and white children. Significant racial differences were noted, with black children having lower HR at preexercise (black children, 97.8 ± 14.7 beats per minute; white children, 105.0 ± 13.3 beats per minute; $P<.04$) and higher peak SBP during exercise (black children, 124.7 ± 25.7 mm Hg; white children, 113.1 ± 24.1 mm Hg; $P<.05$). Black children also showed marginally higher peak DBP during exercise (black children, 72.2 ± 23.7 mm Hg; white children, 64 ± 14.4 mm Hg) and lower recovery HR values (black children, 109.0 ± 13.9 beats per minute; white children, 115.8 ± 13.6 beats per minute) than white children (both $P<.07$).

To examine differences in cardiovascular reactivity to exercise, HR, SBP, and DBP change scores were computed. These means and SDs by race are also presented in Table 2. Heart rate reactivity was computed by subtracting preexercise HR from the peak HR obtained during exercise. The SBP and DBP reactivity scores (ie, ΔSBP, ΔDBP) were also computed by subtracting preexercise values from respective peak values obtained during exercise (ie, peak value minus preexercise values). Similarly, HR, SBP, and DBP recovery change scores were computed by subtracting the recovery value from the respective peak value obtained during exercise (ie, peak value minus recovery values).

These exercise and recovery change scores were then used as the dependent variables in an ANOVA testing the effects of race and gender. There were no gender differences in increases from preexercise to peak exercise, but girls showed marginally smaller decreases in DBP during recovery (boys, −14.5 ± 21.8 mm Hg; girls, −4.7 ± 18.4 mm Hg; $P<.07$). No other gender comparisons of change scores were significant (all $P>.48$).

As predicted, black children showed significantly larger increases in SBP from preexercise to peak exercise than did white children ($P<.04$). There were no racial differences in DBP or HR changes in response to exercise (both $P>.25$). No racial differences in recovery change scores were obtained, indicating that SBP, DBP, and HR declines from peak exercise values were similar for black and white children ($P<.15$, $P<.10$, and $P<.56$, respectively).

Table 1.—Means and SDs of Anthropometric Variables by Race

Anthropometric Variable	White		Black	
	Mean	SD	Mean	SD
Age, y	5.4	0.53	5.5	0.63
Height, cm	111.4	6.20	114.3	6.5
Weight, kg	19.4	3.15	19.9	3.13
Obesity, QI*	15.6	1.80	15.2	1.50
Body surface area, m²†	0.71	0.08	0.74	0.09

*QI indicates the Quetelet index (kg/m²).
†Body surface area was calculated using the West nomogram.[16]

Table 2.—Means and SDs of Hemodynamic Changes for Stages of Exercise by Race*

Hemodynamic Variable	Mean (SD)									
	Preexercise		Peak		Exercise Change		Recovery		Recovery Change	
	W	B	W	B	W	B	W	B	W	B
HR, beats per minute	105.0† (13.3)	97.8 (14.7)	182.2‡ (13.6)	173.3 (12.3)	77.2 (16.5)	75.5 (18.3)	115.8 (13.6)	109.0 (13.9)	66.0 (17.6)	63.5 (14.9)
SBP, mm Hg	92.5 (16.7)	93.0 (14.6)	113.1† (24.1)	124.7 (25.7)	20.6† (21.2)	31.7 (19.6)	98.9 (14.3)	94.8 (14.7)	16.4 (27.9)	27.4 (27.7)
DBP, mm Hg	52.5 (14.2)	55.9 (16.2)	64.0 (14.4)	72.2 (23.7)	12.0 (16.8)	17.0 (16.9)	56.8 (12.6)	55.1 (11.9)	7.6 (17.8)	17.1 (26.4)

*Exercise change equals maximum value minus preexercise value. Recovery change equals maximum value minus recovery value. W indicates white; B, black; HR, heart rate; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
†Racial difference, $P<.05$.
‡Racial difference, $P<.008$.

COMMENT

Consistent with the results of other studies of preadolescents (see Sallis et al[9] for a review), no evidence of gender differences in cardiovascular reactivity was obtained in the present study. Research with adults has generally found greater reactivity to stressors among men, especially for neuroendocrine indices such as catecholamine excretion.[17] There is evidence that reactivity to stress in women may be complexly influenced by hormonal variations, sociocultural and cognitive factors, and stressor qualities such as gender role appropriateness.[18] Hence, gender differences in reactivity may not become apparent until at least adolescence, at which time such factors might become significant.[18] Further research is needed to test this hypothesis and investigate the circumstances under which males and females exhibit different cardiovascular responses to stress.

The girls in the present study did show a trend toward slower recovery of DBP after exercise. Although recovery data are not often analyzed in reactivity studies, it has been postulated that slow autonomic recovery from stress, which is associated with poor aerobic fitness,[19,20] may play a role in the development of cardiovascular diseases.[21] In light of these findings, further investigation is needed of children's cardiovascular recovery from stress and its relationship to cardiovascular risk factors (eg, physical activity and fitness, obesity, type A components).

The only preexercise differences noted were that black children and boys had significantly lower HR than their respective cohorts. Previous studies have reported these racial[22] and gender[18] differences in children's HRs. The underlying physiological and/or environmental mechanisms responsible for these differences have not yet been determined and are topics for future research.

Consistent with previous studies of older children and adolescents,[1,2] black children as young as 4 years of age showed higher peak SBP responses and larger SBP increases to dynamic upright submaximal exercise than did white children, even though they attained lower peak HR. Although the possible influence of life-style behaviors (eg, physical activity), psychological, and other environmental factors cannot be eliminated, the fact that these reactivity differences are apparent at such an early age suggests that genetic and/or other biological mechanisms may play a role in racial differences in cardiovascular reactivity to stress. However, given our relatively small sample size, further research is needed to replicate these findings before definitive conclusions can be drawn.

The underlying hemodynamic mechanism thought to be responsible for blood pressure reactivity to stress in black people is greater systemic vascular resistance rather than high cardiac output.[23,24] Recent findings indicate that this may indeed be the case. Anderson et al[6] found that black college-age adults showed larger increases in blood pressure and forearm vascular resistance to vasoconstrictive cold stimulation than did white adults. Since there were no racial differences in HR changes, larger increases in systemic vascular resistance were inferred to account for these reactivity differences. In response to challenging reaction time tasks, black hypertensives and/or normotensives have been found to exhibit greater calf muscle vascular resistance[25] and greater total peripheral resistance[26] than comparable groups of white people. We recently obtained evidence for racial differences in vascular resistance in a biracial group of 10-year-old boys undergoing dynamic exercise testing.[27] Black boys had significantly higher systemic vascular resistance as calculated from Doppler echocardiographic measurements of cardiac output than did white boys at preexercise, maximum exercise, and recovery. In that study, the children exercised in the supine position. Although there were no significant differences in blood pressure responses between the black and white children, the white children had greater cardiac output at the same physical working capacity levels. Collectively, these findings suggest that greater systemic vascular resistance may account for a black person's exaggerated pressor responses to stress, although the underlying physiological changes (ie, greater vasoconstriction, lesser vasodilation) may vary depending on the type of stressor.

This study indicates that further research on the hemodynamic mechanisms underlying racial differences in blood pressure reactivity to stress is not only warranted but critical to our understanding of the antecedents of essential hypertension. Studies that use a variety of psychological (eg, mental arithmetic, competitive video games, reaction time tasks) and physical (eg, isometric and dynamic exercise, norepinephrine infusion, cold pressor) stressors, and obtain measures of cardiac output and systemic vascular resistance in addition to blood pressure and HR will be helpful in this regard. Finally, longitudinal research on children as young as those in the present study will further our understanding of whether racial differences in cardiovascular reactivity are a function of biologically predisposing factors, environmental experiences, or a combination of both. Information from this research may prove useful in the early identification of individuals at risk for hypertension and may result in more effective primary prevention.

This research was supported by grants HL 35073 and 41781 from the National Heart, Lung and Blood Institute, Bethesda, Md.

The authors wish to express their gratitude to Pamela Hawkins and Laurie Adams for secretarial assistance; Bonnie Hadden for technical assistance; Thomas Rhodes for statistical support; Jennifer Kenrick, Leonteen McNeil, Sherri Budwick, Dale Sussman, and Ellen Wilson for assistance in data collection; and all of the children and families involved in the Study of Children's Activity and Nutrition project.

References

1. Alpert BS, Flood NL, Strong WB, et al. Responses to ergometer exercise in a healthy biracial population of children. *J Pediatr.* 1982;101:538-545.

2. Alpert BS, Dover EV, Booker DL, Martin AM, Strong WB. Blood pressure responses to dynamic exercise in healthy children: black vs. white. *J Pediatr.* 1981;99:556-560.

3. Murphy JK, Alpert BS, Moes DM, Somes GW. Race and cardiovascular reactivity: a neglected relationship. *Hypertension.* 1986;8:1075-1083.

4. Murphy JK, Alpert BS, Willey ES, Somes GW. Cardiovascular reactivity to psychological stress in healthy children. *Psychophysiology.* 1988;25:144-152.

5. Light KC, Obrist PA, Sherwood A, James SA, Strogatz DS. Effects of race and marginally elevated blood pressure on responses to stress.

Hypertension. 1987;10:555-563.

6. Anderson NB, Lane JD, Muranaka M, Williams RB, Houseworth SJ. Racial differences in blood pressure and forearm vascular responses to the cold face stimulus. *Psychosom Med*. 1988;50: 57-63.

7. Roberts J, Rowland M. *Hypertension in Adults 25-74 Years of Age: United States, 1971-1975 Vital and Health Statistics*. Washington, DC: Government Printing Office; 1984:10-15. US Dept of Health and Human Services publication PHS 81-1671, Series II, No. 221.

8. *Health Indicators for Hispanic, Black, and White Americans*. Washington, DC: National Center for Health Statistics; 1984:107-112. US Dept of Health and Human Services publication 84-15761.

9. Sallis JF, Dimsdale JE, Caine C. Blood pressure reactivity in children. *J Psychosom Res*. 1988;32:1-12.

10. Voors AW, Foster TA, Fredichs RR, Webber LS, Berensen GS. Studies of blood pressure in children, ages 5-14 years, in a total biracial community: the Bogalusa heart study. *Circulation*. 1976;54:319-327.

11. Prineas RJ, Gillium RF, Gomez-Marin O. The determinants of blood pressure levels in children: the Minneapolis children's blood pressure study. In: Loggie JMH, Horan MJ, Gaskin AB, Hohn AR, Dunbar JB, Havlik RJ, eds. *NHLBI Workshop on Juvenile Hypertension*. New York, NY: Biomedical Information; 1983:21-35.

12. Schmidt TH, Thierse H, Eschweiler J. Behavioral correlates of cardiovascular reactivity in school children. In: Schmidt TH, Dembroski TM, Blumchen G, eds. *Biological and Psychological Factors in Cardiovascular Disease*. New York, NY: Springer-Verlag NY Inc; 1986:187-227.

13. Matthews KA, Stoney CM. Influences of sex and age on cardiovascular responses during stress. *Psychosom Med*. 1988;50:46-56.

14. Park MK, Menard SM. Accuracy of blood pressure measurement by the Dinamap Monitor in infants and children. *Pediatrics*. 1987;79:907-914.

15. Alpert BS, Flood NL, Balfour IC, Strong WB. Automated blood pressure measurement during ergometer exercise in children. *Cathet Cardiovasc Diagn*. 1982;8:525-533.

16. Berman RE, Vaughn VC, eds. *Textbook of Pediatrics*. 12th ed. Philadelphia, Pa: WB Saunders Co;1979:1814. Figure 29-1.

17. Frankenhauser M, Rouste–von Wright M, Collins A, von Wright J, Sedvall G, Swahn CG. Sex differences in psychoneuroendocrine reactions to examination stress. *Psychosom Med*. 1978;40:334-343.

18. Watkins LO, Eaker E. Population and demographic influences on reactivity. In: Matthews KA, Weiss SM, Detre T, et al, eds. *Handbook of Stress, Reactivity, and Cardiovascular Disease*. New York, NY: John Wiley & Sons Inc; 1986:231-257.

19. Keller S, Seraganian P: Physical fitness and autonomic reactivity to psychosocial stress. *J Psychosom Res*. 1984;28:279-287.

20. Sinyor D, Schwartz SG, Peronnet F, Brisson G, Seraganian P. Aerobic fitness level and reactivity to psychosocial stress: physiological, biochemical, and subject measures. *Psychosom Med*. 1983;45:205-217.

21. Plante TG, Karpowitz D. The influence of aerobic exercise on physiological stress responsivity. *Psychophysiology*. 1987;24:670-677.

22. Shekelle RB, Liu SG, Raynor WJ, Miller R. Racial differences in mean pulse rates of children aged six to eleven years. *Pediatrics*. 1978;61:119-121.

23. Dimsdale JE, Graham RM, Ziegler MG, Zusman RM, Berry CC. Age, race, diagnosis and sodium effects on the pressor response to infused norepinephrine. *Hypertension*. 1987;10:564-569.

24. Falkner B. Is there black hypertension? *Hypertension*. 1987;10:551-553.

25. Fredrikson M. Racial differences in reactivity to behavioral challenge in essential hypertension. *J Hypertens*. 1986;4:325-331.

26. Light K, Sherwood A. Race, borderline hypertension and hemodynamic responses to behavioral stress before and after beta-adrenergic blockade. *Health Psychol*. In press.

27. Arensman FW, Treiber FA, Gruber MP, Strong WB. Exercise-induced differences in cardiac output, blood pressure, and systemic vascular resistance in a healthy biracial population of 10-year-old boys. *AJDC*. 1989;143:212-216.

Authorship

Science reports (1988;242:1130) that they cited an article published in Japan that listed 193 authors from 20 institutions! That prompted them to research the records for authorship, with the following results. In 1986, a report in *Plasma Physics and Controlled Fusion* had 246 authors. The same research group had a report in the *International Atomic Energy Associations' Conference on Plasma Physics and Controlled Nuclear Fusion* in 1986 with 257 authors. In 1987, an article appeared in *Physical Review* that was authored by 108 persons.

We at *AJDC* become excited if more than six authors are named!

Toxoplasmosis Needs Evaluation

An Overview and Proposals

Marjaleena Koskiniemi, MD, PhD; Maija Lappalainen, MD; Klaus Hedman, MD, PhD

Toxoplasmosis is usually an asymptomatic and innocent disease, but in fetuses and immunocompromised hosts it often takes a severe course. *Toxoplasma gondii* exists in host tissues as oocysts, tachyzoites, and cysts. The oocysts are formed in the lining cells of the ileum of the cat and are shed in the feces.[1] The tachyzoites, which are the acute-phase agents, may invade the nucleated cells of all mammals. The tissue cysts contain up to 3000 bradyzoites, which remain alive for the life span of the host.

The oocysts in cat feces become infective in 1 to 5 days and may remain viable for a year. Mammals are infected by oocysts via vectors. *Toxoplasma* is also transmitted by infected meat, eaten raw or poorly cooked, unwashed/unpeeled vegetables and fruit, body secretions (ie, unpasteurized milk and blood transfusions), and transplanted organs.[1]

New aspects of this old parasitic disease that have recently come to light appear to justify a reappraisal of the whole question of the prevalence and significance of toxoplasmosis. The consequences of intrauterine *Toxoplasma* infection are gaining recognition, and toxoplasmosis is diagnosed in growing numbers of patients with immunosuppression due to various causes, such as malignant diseases, organ transplants, and acquired immunodeficiency syndrome (AIDS).[2] Therefore, a reevaluation of toxoplasmosis is needed.

Accepted for publication January 11, 1989.

From the Department of Virology and Children's Hospital, University of Helsinki, Finland.

Reprint requests to the Department of Virology, University of Helsinki, Haartmaninkatu 3, SF-00290 Helsinki, Finland (Dr Koskiniemi).

PATHOGENESIS AND EPIDEMIOLOGY

The parasites are phagocytosed in the ileum or enter body cells, multiply, and cause rupture of the host cells. Necrotic foci are formed around them. Organisms are killed by monocytes and neutrophils, but the tachyzoites remain alive in macrophages and spread via the circulation.

In fetuses, newborn infants, and immunodeficient patients, the control of invasion is impaired. The blood-brain barrier prevents antibodies from reaching the retina and the central nervous system, and so assists the parasite. The host has no defense against organisms inside tissue cysts.[1,3]

No sex differences appear in the occurrence of *Toxoplasma*-specific antibodies, but geographic variation is considerable. The prevalence of these antibodies in pregnant women varies, being 22% to 32% in New York, NY, and London, England, 84% in Paris, France, 12.5% in Oslo, Norway, and 25% in Finland.[4-7]

Primary *Toxoplasma* infection in the mother carries a risk of intrauterine infection of about 20% in the first trimester and about 70% in the last trimester.[7-9] Rough estimates of congenital toxoplasmosis vary from 0.5 to 6.5 cases per 1000 live births.[1,5,6,8,10-12] Accordingly, about 3300 infants with congenital toxoplasmosis are born each year in the United States compared with 130 in Finland.

ACUTE TOXOPLASMOSIS

Toxoplasma infection is asymptomatic in 80% to 90% of cases.[13] It may present as cervical lymphadenopathy.[14] Fever, malaise, night sweats, sore throat, maculopapular rash, hepatosplenomegaly, or atypical lymphocytes may appear.[15] Immunodeficient patients are at great risk of severe or even fatal toxoplasmosis by reactivation of a latent infection.[16] In patients with AIDS, it is the most common cause of opportunistic infection of the central nervous system, causing abscesses, encephalitis or other encephalopathy, cognitive impairment, headache, chorioretinitis, and systemic manifestations. Clinically, apparent *Toxoplasma* encephalitis has been reported to occur in 30% to 40% of patients with AIDS.[17,18]

CONGENITAL TOXOPLASMOSIS

On average, 10% to 15% of infants infected during pregnancy show symptoms neonatally (Table 1).[9,19] There is a generalized infection involving many organs. Periaqueductal and periventricular vasculitis, necrosis, and calcifications are characteristic of congenital toxoplasmosis.[20] The average mortality rate of all infected infants is 1% to 6%.[1,9] Surviving infants suffer from mental retardation or other neurologic deficits. The toxoplasmosis triad—hydrocephalus, chorioretinitis, and intracranial calcifications—is a rare form of congenital toxoplasmosis.[21] Medical treatment of the infected pregnant mother reduces the mortality rate and severity of the disease in the newborn.[22] Infected infants who appear healthy at birth devel-

Table 1.—The Most Common Signs and Symptoms of Congenital Toxoplasmosis Manifesting at Birth

	Signs/Symptoms
Central nervous system involvement	Convulsions, spasticity
	Hypotonia, paralyses
	Chorioretinitis, strabismus, nystagmus
	Deafness, blindness
	Encephalitis
	Hydrocephalus, bulging Fontanelle
	Microcephaly, microphthalmia
Generalized infection	Fever
	Diarrhea, vomiting, eating difficulties
	Breathing difficulties, pneumonia
	Hepatosplenomegaly
	Jaundice, anemia, eosinophilia
	Bleeding tendency
	Lymphadenopathy
	Maculopapular rash
Miscellaneous	Intrauterine growth retardation
	Prematurity
	Hypothermia
	Myocarditis
	Nephrotic syndrome
	Metaphyseal lucency

op chorioretinitis or neurologic symptoms in 80% to 90% of cases by age 20 years.[23,24]

SEROLOGIC DIAGNOSTIC METHODS

Given the nonspecificity of symptoms and the large proportion of nonsymptomatic infections, the diagnosis of toxoplasmosis is usually based on laboratory tests, of which serologic tests are conventional.

1. The Sabin-Feldman Dye Test (DT) is a reference test. It measures IgG class antibodies, which appear within 1 to 2 weeks of the onset of symptoms, increase for 6 to 8 weeks, and persist in declining titers for years. The titer does not correlate with the severity of the disease. The DT is sensitive and specific, but owing to technical difficulties, it has been abandoned in many countries.[20]

2. The indirect immunofluorescence assay, which is simpler than the DT, is now the most widely used test. It may be used to measure antibodies of the IgG class, like the DT, or of the IgM class. Antinuclear antibodies and rheumatoid factor cause false-positive results in the IgM indirect immunofluorescence assay.[25]

3. In the complement fixation test, antibodies become detectable several weeks later than antibodies detected by the DT, and may disappear earlier, but they may remain positive for years. Thus, a negative complement fixation test result does not rule out, and a positive one does not confirm, acute infection.[20]

4. The enzyme-linked immunosorbent assay (ELISA) is a simple and objective test for both IgG and IgM antibodies.[20,26-28]

5. The direct agglutination test (Bio-Merieux, Lyons, France) may be used to detect IgG antibody.[29] It is a simple and inexpensive method for screening of pregnant women but should not be used for measurement of IgM antibodies because nonspecific agglutination is often seen. However, this test has been combined with the ELISA test to detect IgM antibodies, ie, the IgM immunosorbent agglutination assay, which is both specific and sensitive.[26]

6. Immunoblot analysis of antigenic molecules separated in sodium dodecyl sulfate gel electrophoresis is a valuable tool for determining the specificity of the IgG or IgM class antibodies.[30] *Toxoplasma*-specific IgG antibodies react against several antigens with molecular weights of 27 000 to 60 000 d.[30-34] The IgM antibodies react predominantly with proteins of 35 000, 25 000, and 60 000 d.[30,35-37] Reactions with antigenic molecules of 4000 d, 115 000 d, and others have been reported.[34,38]

Antibody determinations should be repeated with a second serum sample obtained 2 to 4 weeks after the initial one. A fourfold or greater rise in titer, or a positive IgM antibody result, is considered diagnostic. A single high IgG titer is of little value in the assessment of the time point of the infection. In a fetus, the sensitivity of a specific IgM antibody finding is low, only 25%.[20] In a newborn, persistent or rising titers of specific IgG, or a positive IgM antibody result, establishes the diagnosis, but the findings are inconsistent and lose their diagnostic significance in regard to congenital infection after about 3 months.[9] In a newborn, antibody titers of cerebrospinal fluid specimens compared with serum levels are helpful in diagnosis.[1]

Immunocompromised patients seldom show a diagnostic rise in antibody titer, and the appearance of specific IgM response is rare.[17,39] Evidence of intrathecal production of specific antibody is considered diagnostic.[17,39,40]

DEMONSTRATION OF ANTIGEN

Antigenic components of *Toxoplasma* may be detected in different specimens for a long period after infection, and even at an early stage.

1. Isolation of the parasite is a specific diagnostic method. *Toxoplasma gondii* is usually isolated in mice, but tissue culture methods have been developed.[1,41] Blood, body fluids, or tissue extracts may be examined. These usually are inoculated into a mouse, which develops *Toxoplasma* infection, as can be confirmed by microscopic examination of tissue extracts. However, the process takes 6 weeks.

2. Enzyme-linked immunosorbent assays have been developed for antigenemia, which may be present during the acute phase of infection with *T gondii*.[42,43] Antigenic components of *T gondii* could be detected in different tissue specimens from the first day of infection in an experimental model. This may prove valuable for a rapid diagnosis. Alternatively, a dot immunobinding assay has been used.[44] The antigen has been detected by spotting samples directly onto nitrocellulose paper. These methods are useful when the diagnosis of toxoplasmosis cannot be made by measuring antibody levels alone.

Antigen detection techniques are valuable in newborns and immunocompromised hosts in whom antibody responses are variable and who often fail to show an IgM response. At birth, demonstration of tachyzoites in the placenta establishes the diagnosis of intrauterine infection, but a negative finding does not always rule it out.[1] In a fetus, demonstration of antigen in amniotic fluid may be positive in 60% of infections, but between weeks 17 and 25 the parasite can be isolated in only 45% of specimens from the amniotic fluid, compared with 70% from fetal blood.[45] In some cases antigens in serum of a fetus or newborn may be detected by immunoblot techniques.

In an immunocompromised host, detection of tachyzoites or antigenic components in brain tissue or cerebrospinal fluid is diagnostic, and may be the only evidence of infection.[39,37,46]

NEW DIAGNOSTIC APPROACHES

Methods have recently been developed for studying the avidity of polyclonal IgG responses elicited by the immunologically complex and large microbial antigens. The IgG from patients with a recent primary *Toxoplasma* infection is eluted off the antigen by hydrogen-bond–dissociating agents in conditions in which the IgG of past immunity mostly remains antigen bound. In studies comprising 16 patient serum samples and 21 control serum samples, this straightforward assay distinguished all samples obtained within a few months of the onset of toxoplasmosis from the patients with preexisting *Toxoplasma* immunity.[47] We call this test *avidity-ELISA*. For comparison, very similar assays have reached the level of routine diagnostic use for recent primary rubella virus infections, and for their separation from rubella reinfections.[48-50]

In early pregnancy, the avidity-ELISA should help in timing the *Toxoplasma* infection in cases with high IgG titer and positive IgM. This is important for treatment of the mother if the infection appears recent. In general, the advent of such techniques could facilitate the distinctions between the primary infections and both reactivations and prolonged positivity of IgM tests.

THERAPY FOR TOXOPLASMOSIS

Immunocompetent adults with lymphadenopathy caused by toxoplasmosis are n ot treated unless symptoms are unusually severe or persistent. Immunodeficient patients with toxoplasmosis need prompt therapy. The loading dose of pyrimethamine for adults is 100 mg/d divided into two doses, combined with sulfadiazine (75 mg/kg per day up to 4 g/d for 2 days). Thereafter, pyrimethamine (25 mg/d or every other day) and sulfadiazine (100 mg/kg per day up to 8 g/d divided into two doses) are given for 2 to 4 months; for immunodeficient patients, they are given for 6 months or longer. The maintenance dosage of pyrimethamine may be raised to 50 mg/d.[20,45]

Both pyrimethamine and sulfadiazine are folinic acid antagonists and may cause bone marrow depression. Administration of folinic acid may diminish this effect.[20] Pyrimethamine may also cause gastrointestinal symptoms, headache, and a bad taste in the mouth. The peripheral blood picture, hemoglobin, hematocrit, and total and differential white blood cell counts, including platelets, should be monitored twice a week during medication.

The combination therapy of trimethoprim and sulfamethoxazole may have fewer side effects and produce a better response.[51] Ocular toxoplasmosis may be treated with clindamycin.[52] Systemic corticosteroid therapy is indicated if lesions involve the macula or optic nerve.

During pregnancy, spiramycin therapy (3 g/d for 3 weeks followed by an interruption for 2 weeks) diminishes the risk of fetal infection by as much as 50%.[9,22] In a recent report, spiramycin was administered continuously without interruption.[45] It achieves high concentrations in the placenta. No teratogenic effects have been reported in humans. It is widely used in France, Austria, and Portugal. If the fetus is infected, pyrimethamine and sulfadoxine (25 mg and 500 mg, respectively) are administered every 10 days in addition to the daily spiramycin.[45] In some cases, pyrimethamine and sulfadiazine (50 mg and 3 g, respectively) have been given for 3 weeks, alternating with the daily spiramycin for 3 weeks. Folinic acid is included in both regimens.

The therapy of congenitally infected children depends on signs and symptoms (Table 2). Late manifestations may thus be prevented in both symptomatic and asymptomatic children.

Table 2.—Therapy for Congenital Toxoplasmosis

Condition	Treatment
Manifest congenital toxoplasmosis*	Pyrimethamine (0.5-1.0 mg/kg per day orally in 2 doses) every second, third, or fourth day Sulfadiazine (50-100 mg/kg per day orally in 2 doses) Folinic acid (5 mg/kg per day) during pyrimethamine treatment Spiramycin (100 mg/kg per day) orally in 2 doses
Subclinical congenital toxoplasmosis	Same treatment as above, lasting at least 6 mo
Healthy newborn with negative serology; mother shown to have acquired toxoplasmosis during pregnancy	Pyrimethamine and sulfadiazine as above for 21 d and spiramycin for 30-45 d†
Healthy newborn; mother has high titer but timing of infection is undefined	Spiramycin as above for 30-45 d†

*Treatment is continued for first year of life in alternating courses: pyrimethamine and sulfadiazine for 21 days and spiramycin for 30 to 45 days. However, each child's treatment must be planned individually.
†Await laboratory results for *Toxoplasma*-specific antibodies.

REPORT OF PATIENTS

In a recent retrospective survey, we detected 32 children with the diagnosis of toxoplasmosis treated at the Children's Hospital, University of Helsinki, Finland, in the period 1963 to 1984. The age range was 0 to 15 years. In 10, the diagnosis was confirmed by age 1 month. In 21 patients, a serologic confirmation was obtained. In 11, the diagnosis was based on history and characteristic clinical picture without serologic confirmation. During this 22-year period, the birth rate in the area was 330 000, indicating an incidence of 1 case per 10 000 newborns. No screening tests were done during pregnancy; thus, all diagnoses were made after birth and as such were accidental.

Table 3.—The Most Common Signs and Symptoms in Children With Congenital Toxoplasmosis Treated at the Children's Hospital, University of Helsinki, Finland

Signs/Symptoms	No. (%) of Patients (N = 32)
Neurologic symptoms	25 (78)
Convulsions	12
Hypotonia/hypertonia	10
Absences	4
Other	2
Chorioretinitis	18 (56)
Bilateral	8
Unilateral	9
Suspected	1
Hydrocephalus	9 (28)
Appeared by age 1 mo	7
Hepatosplenomegaly	6 (19)
Classic triad (hydrocephalus, hepatosplenomegaly, and intracranial calcifications)	1 (3)

Neurologic symptoms appeared in 78% of patients, mainly convulsions, but muscular hypertonia or hypotonia was also seen. In addition, chorioretinitis, hydrocephalus, and hepatomegaly appeared, as well as abnormalities in laboratory examination results (Tables 3 and 4).

Five (16%) of the 32 children died, 4 at ages 33 to 41 days and 1 at age 7 years. Three

Table 4.—The Most Common Laboratory and Radiologic Findings in Children With Congenital Toxoplasmosis Treated at the Children's Hospital, University of Helsinki, Finland

Findings	No. (%) of Patients (N=32)
Abnormal electroencephalogram	25 (78)
Cerebrospinal fluid alterations	13 (41)
Raised protein concentration	11 (34)
Lymphocytosis	10 (31)
Peripheral blood pathology	9 (28)
Anemia	3 (9)
Thrombocytopenia	1 (3)
Eosinophilia	2 (6)
Raised total IgM concentration in serum	4 (13)
Intracranial calcifications	11 (34)

children (9%) needed permanent hospitalization. Three of those who died and all the severely damaged children had received pyrimethamine and sulfadiazine therapy. Of the whole series, 47% of the patients received medication. Our results indicate poor therapeutic efficacy. In no case was medication started prenatally.

Additionally, 230 children were treated at the Children's Hospital for convulsions of unknown cause in the period 1980 to 1981. Antibody tests against *T gondii* had been performed on 154 children. No antibody tests were done on the other 76 children. No positive diagnostic titers were seen.

COMMENT

Prevention of Toxoplasmosis

Prevention of and specific therapy for *Toxoplasma* infection are important for seronegative pregnant women and immunodeficient patients. Infection is prevented bv avoiding ingestion of and contact with cysts or sporulated oocysts (Table 5).[14] Immunodeficient patients with toxoplasmosis as well as pregnant women with primary *Toxoplasma* infection and children with congenital infection should be treated.

Congenital Toxoplasmosis

Congenital toxoplasmosis appears to have been a latent problem until now. Sequelae of *Toxoplasma* infection during pregnancy are much more severe and widespread than has been previously appreciated.[23,53] Infected children, if they survive, suffer from progressive

Table 5.—Prevention of *Toxoplasma* Infection During Pregnancy

- Meat must be cooked thoroughly at 66°C at least
- When handling raw meat, touching the mucous membranes of the mouth and eye must be avoided; after handling raw meat, hands and table surfaces must be washed carefully
- Uncooked eggs should be avoided
- The access of insects to foodstuffs must be prevented
- Vegetables and fruit must be washed and, better still, peeled
- In gardening, gloves should be used
- Pregnant women should avoid all possible contact with cat feces, disinfection of cat litter box, and sandboxes used by cats
- Travelling to areas with a high incidence of toxoplasmosis must be avoided during pregnancy

symptoms in the vast majority of cases and the cause of their problems has remained untraced. The only way to identify patients with congenital toxoplasmosis is reliable antibody screening during pregnancy.[54]

The incidence of toxoplasmosis during pregnancy appears to be 3 to 6 cases per 1000 live births in "high-risk" countries, while in "low-risk" countries, it is 1 to 2 cases.[11] The great excess of seronegative mothers in "low-risk" countries, however, suggests that the prevalence of acute primary infection during pregnancy may be the same as in "high-risk" countries.

Screening of Pregnant Women

In France and Austria, national health policy has long dictated measurement of antibody levels during pregnancy.[54,55] In Norway, also, a screening program is planned (B. Stray-Pedersen, MD, personal communication, 1987). In the United States, an urgent plea has been made for screening programs.[2] Care for the victims of congenital toxoplasmosis requires millions of dollars every year. The need for prospective trials of the benefits and costs of screening programs is underlined.

The goal of screening programs is to identify seronegative pregnant women. In an optimal protocol, all pregnant mothers would be tested early in pregnancy, and seronegative women thereafter monthly or in every trimester, at least. In this way, the onset of infection could be timed and appropriate therapy be instituted after determining whether the fetus is infected or not. Therapeutic abortion is possible for those women who become infected during the first or early in the second trimester (about 50%).[56] Prenatal diagnosis and therapy appear essential, although the mode of medication is uncertain, ie, whether it should be a combination of drugs, whether it should be continuous or intermittent, and how long it should be administered.

It is important to distinguish between primary infection and reactivation, and to assess the exact time of the primary infection. First, to make a diagnosis of primary infection by showing a seroconversion of IgG antibodies, one must obtain the primary sample of paired serum samples at a very early stage of the infection. Second, *Toxoplasma* IgM antibodies in many patients with primary infection remain detectable for a year or longer.[36] Thus, in asymptomatic individuals with stable titers of *Toxoplasma* IgG antibodies, positive IgM results are not easy to interpret. Such cases may lead to confusion in a large-scale prenatal serologic screening program. Tests for the avidity of specific IgG appear promising in solving this problem.

CONCLUSION

Diagnostic uncertainty has evidently diminished the interest in congenital toxoplasmosis.[10] Routine antibody screenings are not diagnostic in children with sequelae of intrauterine infection.[57] New approaches are needed. Sensitive and specific ELISA tests are widely used. Rapid techniques confirm the presence of *Toxoplasma* antigens in a few days. With the immunoblot test, antibodies against different antigenic molecules can be measured, or different antigenic components may be found in serum specimens. Presumably, it will soon become possible to distinguish acute infection from old immunity.

The significance of *Toxoplasma* infections has increased enormously since the number of patients with immunodeficiency, especially those with AIDS and with organ transplants, has increased. *Toxoplasma* infections account for one third of the infections in patients with AIDS.[17,58] In such pa-

tients, sophisticated antigen detection methods are needed.[37]

The time has come for prospective studies using this new methodology to ascertain the incidence, manifestations, and therapeutic possibilities of *Toxoplasma* infections and to draw up plans for future programs for economic as well as humane considerations.[2,56] Careful search should be made for children with ongoing toxoplasmosis originating from intrauterine infection, as well as children and adults with immunodeficiency, or immunosuppression, because *Toxoplasma* infections are serious but treatable diseases.

References

1. Remington JS, Desmonts G. Toxoplasmosis. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. Philadelphia, Pa: WB Saunders Co; 1983:191-332.
2. McCabe R, Remington JS. Toxoplasmosis: the time has come. *N Engl J Med*. 1988;318:313-315.
3. Weber F. The cerebral lesions in congenital toxoplasmosis: study of 9 personal cases and 61 cases in the literature. *Helv Pediatr Acta*. 1983;48(suppl):1-51.
4. Grönroos P. *Studies on* Toxoplasma *and the Serology of Toxoplasmosis*. Helsinki, Finland: University of Helsinki; 1956. Dissertation.
5. Stagno S. Congenital toxoplasmosis: marginal comment. *AJDC*. 1980;134:635.
6. Stray-Pedersen B. A prospective study of acquired toxoplasmosis among 8043 pregnant women in the Oslo area. *Am J Obstet Gynecol*. 1980;136:399-406.
7. Ulmanen I, Leinikki P. The role of pet cats in the seroepidemiology of toxoplasmosis. *Scand J Infect Dis*. 1975;7:67-71.
8. Couvreur J, Desmonts G. Congenital and maternal toxoplasmosis: a review of 300 congenital cases. *Dev Med Child Neurol*. 1962;4:519-530.
9. Desmonts G, Couvreur J. Congenital toxoplasmosis: a prospective study of 378 pregnancies. *N Engl J Med*. 1974;290:1110-1116.
10. Turunen H, Nurmi T, Lehtikangas M. Synnynnäinen toksoplasmoosi. *Duodecim*. 1985; 101:2423-2427.
11. Williams K, Scott J, Macfarlane D. Congenital toxoplasmosis: a prospective survey in the west of Scotland. *J Infect*. 1981;3:219-229.
12. Thalhammer O. Die angeborene Toxoplasmose. In: Kirchhoff H, Kräubig H, eds. *Toxoplasmose: Praktische Fragen und Ergebnisse*. Stuttgart, West Germany: Georg Thieme Verlag; 1966:151-173.
13. Remington JS. Toxoplasmosis in an adult. *Bull NY Acad Med*. 1974;50:211.
14. Siim JC. Epidemiological aspects of toxoplasmosis. In: *Proceedings of the Sixth International Congress of Pediatrics*. Zurich, Switzerland: 1950:365-367.
15. Kean BH. Clinical toxoplasmosis: 50 years. *Trans R Soc Trop Med Hyg*. 1972;66:549-571.
16. Ruskin J, Remington JS. Toxoplasmosis in the compromised host. *Ann Intern Med*. 1971; 74:22-36.
17. Luft BJ, Remington JS. Toxoplasmic encephalitis. *J Infect Dis*. 1988;157:1-6.
18. Navia BA, Petito CK, Gold JWM, Cho E-S, Jordan BD, Price RW. Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: clinical and neuropathological findings in 27 patients. *Ann Neurol*. 1986;19:224-238.
19. Alford CA Jr, Stagno S, Reynolds DW. Congenital toxoplasmosis: clinical, laboratory, and therapeutic considerations, with special reference to subclinical disease. *Bull NY Acad Med*. 1974;50:160-181.
20. McCabe R, Remington J. The diagnosis and treatment of toxoplasmosis. *Eur J Clin Microbiol*. 1983;2:95-104.
21. Wolf A, Cowen D, Paige B. Human toxoplasmosis: occurrence in infants as an encephalomyelitis verification by transmission to animals. *Science*. 1939;89:226-227.
22. Desmonts G, Couvreur J. Congenital toxoplasmosis: a prospective study of the offspring of 542 women who acquired toxoplasmosis during pregnancy: pathophysiology of congenital disease. In: *Perinatal Medicine, 6: European Congress of Vienna, 1978*. Stuttgart, West Germany: Georg Thieme Verlag; 1979:51-60.
23. Koppe J, Loewer-Sieger D, de Roever-Bonnet H. Results of 20-year follow-up of congenital toxoplasmosis. *Lancet*. 1986;1:254-256.
24. Wilson C, Remington J. Development of adverse sequelae in children born with subclinical congenital *Toxoplasma* infection. *Pediatrics*. 1980; 66:767-774.
25. Filice G, Yeager A, Remington J. Diagnostic significance of immunoglobulin M antibodies to *Toxoplasma gondii* detected after separation of immunoglobulin M from immunoglobulin G antibodies. *J Clin Microbiol*. 1980;12:336-342.
26. Desmonts G, Naot Y, Remington J. Immunoglobulin M-immunosorbent agglutination assay for diagnosis of infectious diseases: diagnosis of acute congenital and acquired *Toxoplasma* infections. *J Clin Microbiol*. 1981;14:486-491.
27. Naot Y, Barnett E, Remington J. Method for avoiding false-positive results occurring in immunoglobulin M enzyme-linked immunosorbent assays due to presence of both rheumatoid factor and antinuclear antibodies. *J Clin Microbiol*. 1981; 14:73-78.
28. Naot Y, Desmonts G, Remington J. IgM enzyme-linked immunosorbent assay test for the diagnosis of congenital *Toxoplasma* infection. *J Pediatr*. 1981;98:32-36.
29. Desmonts G, Remington J. Direct agglutination test for diagnosis of *Toxoplasma* infection. *J Clin Microbiol*. 1980;11:562-568.
30. Sharma SD, Mullenax J, Araujo FG, Erlich HA, Remington JS. Western blot analysis of the antigens of *Toxoplasma gondii* recognized by human IgM and IgG antibodies. *J Immunol*. 1983;131:977-983.
31. Partanen P, Turunen HJ, Paasivuo R, Forsblom E, Suni J, Leinikki PO. Identification of antigenic components of *Toxoplasma gondii* by an immunoblotting technique. *FEBS Lett*. 1983; 158:252-254.
32. Remington JS, Araujo FG, Desmonts G. Recognition of different *Toxoplasma* antigens by IgM and IgG antibodies in mothers and their congenitally infected newborns. *J Infect Dis*. 1985; 152:1020-1024.
33. Potasman I, Araujo FG, Desmonts G, Remington JS. Analysis of *Toxoplasma gondii* antigens recognized by human sera obtained before and after acute infection. *J Infect Dis*. 1986:154;650-657.
34. Potasman I, Araujo FG, Thulliez P, Desmonts G, Remington JS. *Toxoplasma gondii* antigens recognized by sequential samples of serum obtained from congenitally infected infants. *J Clin Microbiol*. 1987;25:1926-1931.
35. Partanen P, Turunen H, Paasivuo R, Leinikki P. Immunoblot analysis of *Toxoplasma gondii* antigen by human immunoglobulins G, M, and A antibodies at different stages of infection. *J Clin Microbiol*. 1985;20:133-135.
36. Herbrink P, van Loon AM, Rotmans JP, van Knapen F, van Dijk M. Interlaboratory evaluation of indirect enzyme-linked immunosorbent assay, antibody capture enzyme-linked immunosorbent assay, and immunoblotting for detection of immunoglobulin M antibodies to *Toxoplasma gondii*. *J Clin Microbiol*. 1984;25:100-105.
37. Weiss LM, Udem SA, Tanowitz H, Wittner M. Western blot analysis of the antibody response of patients with AIDS and *Toxoplasma* encephalitis. *J Infect Dis*. 1988;157:7-12.
38. Lindenschmidt EG. Demonstration of immunoglobulin M class antibodies to *Toxoplasma gondii* antigenic component p35 000 by enzyme-linked antigen immunosorbent assay. *J Clin Microbiol*. 1986;24:1045-1049.
39. Hakes TB, Armstrong D. Toxoplasmosis: problems in diagnosis and treatment. *Cancer*. 1983;52:1535-1540.
40. Potasman I, Resnick L, Luft BJ, Remington JS. Intrathecal production of antibodies against *Toxoplasma gondii* in patients with toxoplasmic encephalitis and the acquired immunodeficiency syndrome. *Ann Intern Med*. 1988;108:49-51.
41. Chang CH, Stulberg C, Bollinger RO, et al. Isolation of *Toxoplasma gondii* in tissue culture. *J Pediatr*. 1972;81:790-791.
42. Araujo FG, Remington JS. Antigenemia in recently acquired acute toxoplasmosis. *J Infect Dis*. 1980;141:144-150.
43. Turunen HJ. Detection of soluble antigens of *Toxoplasma gondii* by a four-layer modification of an enzyme immunoassay. *J Clin Microbiol*. 1983;17:768-773.
44. Brooks RG, Sharma SD, Remington JS. Detection of *Toxoplasma gondii* antigens by a dot-immunobinding technique. *J Clin Microbiol*. 1985;21:113-116.
45. Daffos F, Forestier F, Capella-Pavlovsky M, et al. Prenatal management of 746 pregnancies at risk for congenital toxoplasmosis. *N Engl J Med*. 1988;318:271-275.
46. Embil JA, Covert AA, Howes WJ, Tanner CE, Staudt M. Visualization of *Toxoplasma gondii* in the cerebrospinal fluid of a child with malignant astrocytoma. *Can Med Assoc J*. 1985;133:213-214.
47. Hedman K, Lappalainen M, Seppälä I, Mäkelä O. Recent primary *Toxoplasma* infection indicated by a low avidity of specific IgG. *J Infect Dis*. In press.
48. Inouye S, Hasegawa A, Matsumo S, Katow S. Changes in antibody avidity after virus infections: detection by an immunosorbent assay in which a mild protein-denaturating agent is employed. *J Clin Microbiol*. 1984;20:525-529.
49. Hedman K, Seppälä I. Recent rubella virus infection indicated by a low avidity of specific IgG. *J Clin Immunol*. 1988;8:214-221.
50. Rousseau S, Hedman K. Rubella infection and reinfection distinguished by avidity of IgG. *Lancet*. 1988;1:1108-1109.
51. Norrby R, Eilard T, Svedhem A. Treatment of toxoplasmosis with trimethoprim-sulphamethoxazole. *Scand J Infect Dis*. 1975;7:72-75.
52. Ferguson J. Clindamycin therapy for toxoplasmosis. *Ann Ophthalmol*. 1981;13:95-100.
53. Koppe J, Kloosterman G. Congenital toxoplasmosis: long-term follow-up. *Padiatr Padol*. 1982;17:171-179.
54. Desmonts G, Daffos F, Forestier F. Prenatal diagnosis of congenital toxoplasmosis. *Lancet*. 1985;1:500-503.
55. Coradello H, Thalhammer O. Toxoplasmosescreening bei Schwangeren in Österreich. *Z Geburtshilfe Perinatol*. 1984;188:197-211.
56. Wilson C, Remington J. What can be done to prevent congenital toxoplasmosis? *Am J Obstet Gynecol*. 1980;138:357-363.
57. Stagno S. Congenital toxoplasmosis. *AJDC*. 1980;134:635-637.
58. Snider WD, Simpson DM, Neilsen S, et al. Neurologic complications of the acquired immunodeficiency syndrome: analysis of 50 patients. *Ann Neurol*. 1983;14:403-418.

Congratulations, Jackie...

Gold Medal Winner!

Lederle Biologicals is delighted to have sponsored Jackie DiLorenzo at the 1988 Paralympic Games in Seoul, Korea.

Overcoming stiff competition from the best wheelchair table tennis players in the world, Jackie brought home a Gold Medal!

This supreme accomplishment is the result of long-term dedication to her sport, combined with the determination to overcome the effects of poliomyelitis.

This dreaded disease struck Jackie before ORIMUNE became available, leaving her paralyzed from the waist down.

Like Jackie, Lederle Biologicals is fully dedicated to a long-term commitment: the protection of America's children from the ravages of polio.

Please see following page for brief summary of prescribing information.

Orimune®
Poliovirus Vaccine Live Oral Trivalent

Lederle Biologicals
® Protecting Families Through Immunization®

Poliovirus Vaccine
Live Oral Trivalent
ORIMUNE®

A Brief Summary

Please see package insert for full description, directions for use, and references.

INDICATIONS: *For prevention of poliomyelitis caused by Poliovirus Types 1, 2, and 3.*
CONTRAINDICATIONS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

ORIMUNE *must not* be administered to patients with immune deficiency diseases such as combined immunodeficiency, hypogammaglobulinemia, and agammaglobulinemia. It would also be prudent to withhold ORIMUNE from siblings of a child known to have an immunodeficiency syndrome or from children in a family which has a history of immunodeficiency until immune status of all members is determined. Further, ORIMUNE *must not* be administered to patients with altered immune states, such as those occurring in thymic abnormalities, leukemia, lymphoma, or generalized malignancy or by lowered resistance from therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation. All persons with altered immune status should avoid close household-type contact with recipients of the vaccine for at least six to eight weeks. Inactivated poliovirus vaccine (IPV) is preferred for immunizing all persons in the above described circumstances.

WARNINGS: *Under no circumstances should this vaccine be administered parenterally.*

Administration of the vaccine should be postponed or avoided in those experiencing any acute illness and in those with any advanced debilitated condition or persistent vomiting or diarrhea.

Other viruses (including poliovirus and other enteroviruses) may interfere with the desired response to this vaccine, since their presence in the intestinal tract may interfere with the replication of the attenuated strains of poliovirus in the vaccine.

PRECAUTIONS: It would seem prudent not to administer trivalent oral poliovaccine (OPV) shortly after Immune Globulin (IG) unless such a procedure is unavoidable, for example, with unexpected travel to or contact with epidemic areas or endemic areas. If OPV is given with or shortly after IG, the dose probably should be repeated after three months if immunization is still indicated.

The vaccine is not effective in modifying or preventing cases of existing and/or incubating poliomyelitis.

Use in Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Poliovirus vaccine live oral trivalent. It is also not known whether OPV can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Although there is no convincing evidence documenting adverse effects of either OPV or IPV on the developing fetus or pregnant woman, it is prudent on theoretical grounds to avoid vaccinating pregnant women. However, if immediate protection against poliomyelitis is needed, OPV is recommended. (See CONTRAINDICATIONS and ADVERSE REACTIONS.)

ADVERSE REACTIONS: Paralytic disease following the ingestion of live poliovirus vaccines has been, on rare occasion, reported in individuals receiving the vaccine (see, for example, CONTRAINDICATIONS), and in persons who were in close contact with vaccinees. The vaccine viruses are shed in the vaccinee's stools for at least six to eight weeks as well as via the pharyngeal route. Most reports of paralytic disease following ingestion of the vaccine or contact with a recent vaccinee are based on epidemiological analysis and temporal association between vaccination or contact and the onset of symptoms. Most authorities believe that a causal relationship exists. Prior to administration of the vaccine, the attending physician should warn or specifically direct personnel acting under his authority to convey the warnings to the vaccinee, parent, guardian, or other responsible person of the possibility of vaccine-associated paralysis, particularly to susceptible family members and other close personal contacts. The Centers for Disease Control report that during 1972 to 1983, approximately 278.8 million OPV doses were distributed in the United States. During this same period, 87 vaccine-associated cases in apparently immunologically normal individuals were reported. Thirty-two occurred among vaccine recipients (one case per 8.7 million OPV doses distributed), and 55 cases occurred among household and nonhousehold contacts of vaccinees (1 case per 5.1 million doses distributed). Sixteen other vaccine-associated cases have been reported in persons (recipients or contacts) with immune deficiency conditions.

Because the number of susceptible vaccine recipients or contacts of recipients is not known, the true risk of vaccine-associated poliomyelitis is impossible to determine precisely.

When the attenuated vaccine strains are to be introduced into a household with adults who have not been adequately vaccinated or whose immune status cannot be determined, the risk of vaccine-associated paralysis can be reduced by giving these adults one dose of IPV per month for three months before the children receive *Poliovirus vaccine live oral trivalent* ORIMUNE®. The children may receive the first dose of ORIMUNE at the same visit that the adult receives the third dose of IPV. The CDC reports that no paralytic reactions to IPV are known to have occurred since the 1955 cluster of poliomyelitis cases caused by vaccine that contained live poliovirus that had escaped inactivation.

The ACIP states: "Because of the overriding importance of ensuring prompt and complete immunization of the child and the extreme rarity of OPV-associated disease in contacts, the Committee recommends the administration of OPV to a child regardless of the poliovirus-vaccine status of adult household contacts. This is the usual practice in the United States. The responsible adult should be informed of the small risk involved. An acceptable alternative, if there is a strong assurance that ultimate, full immunization of the child will not be jeopardized or unduly delayed, is to immunize adults according to the schedule outlined above before giving OPV to the child."

The ACIP has concluded that "Oral polio vaccine remains the vaccine of choice for primary immunization of children."

Rev. 8/86

Lederle Biologicals
Protecting Families Through Immunization®

Lederle Laboratories, A Division of American Cyanamid Company, Wayne, New Jersey 07470. © 1989 Lederle Laboratories 181-9

PEDIATRICIANS

North Dade Health Center/ Jackson North Maternity Center/ JMH Health Plan

M.D. with current Florida license required. Board eligible with experience in Pediatrics required. Board certified preferred.

We offer an excellent salary and benefits package. For employment consideration, please apply in person or send resume to: **Jackson Memorial Hospital, Employment Office, Park Plaza L-301, 1611 N.W. 12th Avenue, Miami, FL 33136.**

UNIVERSITY OF MIAMI/ JACKSON MEMORIAL HOSPITAL

THE EMPLOYEES' CHOICE

Equal Opportunity/Affirmative Action Employer
The only Florida hospital in the nation's top 25!

STREP TEST™
SHEEP BLOOD AGAR PLATES
LABORATORY CULTURE MATERIALS

- BACITRACIN DISKS
- URI-DIP® URINE CULTURE MATERIALS
- DELUXE INCUBATORS
- DISPENSERS
- INNOCULATING LOOPS
- SWABS

AVAILABLE FROM:
UNIVERSAL BIOLOGICAL LABS
DIAGNOSTIC DIVISION OF:
NATIONAL BIOLOGICAL CORPORATION

1532 ENTERPRISE PARKWAY
TWINSBURG, OHIO 44087
(216) 425-8180
OUTSIDE OHIO: 1-800-338-5045
IN OHIO: 1-800-227-6294

ORDER TODAY
FOR IMMEDIATE DELIVERY

Continuing Medical Education
Continuing Medical Education
Continuing Medical Education
Continuing Medical Education
Continuing Medical Education

On Call

- Diagnostic Support.
- Journals.
- Drug Interactions.
- News.
- And, more.

As close as your own PC.
For more information, call
1-800-426-2873

AMA | Net®

Adolescence

What Is Normal?

Daniel Offer, MD; Eric Ostrov, JD, PhD; Kenneth I. Howard, PhD

• **We present in some detail what constitutes normal behavior, or mental health, among teenagers. Our data are based on the results of a specially devised psychological questionnaire by one of us (D.O.). This questionnaire has been shown to reliably distinguish mentally healthy from psychiatrically disturbed populations. Results are presented across three decades (1960s, 1970s, and 1980s), across genders, and across the high school years. A conceptual framework is presented to help the clinician working with adolescents to understand the fluctuation in psychopathology among youth. Adolescent density in the total population is shown to be a significant factor in determining the rate of disturbance among teenagers. Our research findings demonstrate that the rate of behavioral disturbance among adolescents is the same as in other parts of the life cycle. The clinician working with adolescents tends to underestimate the severity of adolescent problems because of the near-universal belief that all adolescents undergo "adolescent turmoil." We have found that adolescents who are experiencing turmoil need professional help.**

(*AJDC*. 1989;143:731-736)

To many (if not most) health professionals, adolescence is the most stressful and turbulent of all stages in the life cycle.[1-4] Adults, in general, seem to hold the same view.[5] Despite the prevalence and tenacity of this belief, it seems to have little empirical support. One prevailing belief about teenagers is that they are clearly in turmoil, ie, in more turmoil than persons in any other developmental stage. To our knowledge, no study has ever compared the degree of stress during adolescence with that of any other phase of the life cycle.

Similarly, it might be thought that the rate of psychiatric disturbance among teenagers is higher than that of any other period in the life cycle. According to our recent epidemiologic studies, the prevalence of mental disorder among adolescents is about 20%.[6] Studies of adults show a mental disorder prevalence rate almost identical to that shown by adolescents.[7-11] Much has been written about adolescent suicide. Media attention tends to confirm consensus that teenagers have, compared with persons of other ages, an exceedingly high rate of suicide. However, adolescents' suicide rate is lower than that shown by any other age group (with the exception, of course, of prepubertal children).[12] Despite periodic media attention to the adolescent suicide, data show that, in recent years, the adolescent suicide rate has decreased, a result we predicted based on theory.[12] Also despite recent declines in drug and alcohol abuse among teenagers,[13] this abuse remains a serious problem. It is ambiguous whether the rate of substance abuse is higher among teenagers than among older age groups. Adolescents may be more prone to experiment with drugs, while adults may be more prone to abuse alcohol.

An especially persistent belief about teenagers is that they are worse off than preceding generations of teenagers (particularly that generation of teenagers the current group of adults was part of). While it is hard to objectively compare the degree of adolescents' stress to the stress adolescents had in yesteryear, our data, as we shall see, do not indicate that the 1980s were more stressful for teenagers than were previous decades.

To learn about adolescents, our approach is data oriented and epidemiologic. We reject the idea that one can learn about teenagers by saying what they probably are like based on a particular theory, or for that matter by extrapolating from the reminiscences about one's adolescent experiences as adults in treatment. We also reject the idea that one can learn about adolescents by generalizing from the experiences of that highly select group of teenagers who come for or are brought to receive psychiatric help. Theory can, however, help shape expectations about teenagers that can be empirically tested. For instance, a recent systematic study by Enright et al,[14] based on careful ratings of 100 years of articles in the psychological literature, demonstrated ideologic bias in approaches to understanding adolescent psychology. In times of economic depression, they showed that theories emerge that portray adolescents as "immature, psychologically unstable, and in need of prolonged participation in the educational system." In contrast, during wartime, the psychological competence of adolescents is stressed.

Easterlin's "baby-boom–baby-bust theory" is particularly instructive.[15] According to that theory, the higher the proportion of adolescents to the total US population, the more problems adolescents will have. The reasons for this effect are doubtful—it could be that high proportions create increased occasions for negative comparisons for less able adolescents, or it could be that high proportions create competition for scarce resources such as schools or sports facilities. But the true test of this theory is empirical. We used[16] this theory to predict rates of suicide among adolescents.

METHODS AND SUBJECTS

Instrument

Data presented are based on studies using the Offer Self-Image Questionnaire (OSIQ).

Accepted for publication January 19, 1989.

From the Center for the Study of Adolescence, Michael Reese Hospital and Medical Center (Drs Offer and Ostrov), and the Department of Psychiatry, Pritzker School of Medicine, The University of Chicago (Dr Offer), Chicago, Ill; and the Department of Psychology, Northwestern University, Evanston, Ill (Dr Howard).

Presented at the AMA/Duke University Conference on Adolescent Health, Durham, NC, June 9, 1988.

Reprint requests to the Center for Study of Adolescence, Michael Reese Hospital and Medical Center, Lake Shore Drive at 31st Street, Chicago, IL 60616 (Dr Offer).

The OSIQ is a self-descriptive personality test that can be used for measuring the adjustment of adolescents between the ages of 13 and 19 years. It contains 130 items that measure adjustment in 12 areas that are important in the psychological world of the adolescent. The questionnaire was originally developed in 1962 by Offer et al[17,18] to provide a reliable, objective way of selecting a representative group of modal or "normal" adolescents from a larger group of high school students. The OSIQ has since been used in many studies and has been administered to more than 30 000 adolescents. The populations studied include the following: males and females; young and old; urban and suburban; normal, delinquent, and eating disordered; disturbed and physically ill; learning-disabled students; and adolescents from nine countries beside the United States.

Our particular operational approach rests on two major assumptions. First, it is necessary to evaluate the adolescent's functioning in multiple areas because one can master an aspect of one's world while failing to adjust in another. Second, the psychological sensitivity of the adolescent is sufficiently acute to allow us to utilize self-description. Empirical work with the OSIQ has validated these assumptions.

Table 1.—Composition of the Three Samples*

	Young (13-15 y)		Older (16-19 y)	
Decade	M	F	M	F
1960s	290	28	129	145
1970s	212	276	373	524
1980s	123	123	123	123

*Most of the subjects were middle-class adolescents, although the last two decades included subjects from the inner-city and rural areas.

Description of the 12 OSIQ Scales

Impulse Control.—This scale measures the extent to which the ego of the adolescent is strong enough to ward off the various pressures that exist in the external and internal environments. (Negative example: I carry many grudges. Positive example: I can take criticism without resentment.) A low standard score suggests a person whose defensive structure is poorly organized. He or she has low frustration tolerance and often acts on impulse. A high standard score suggests a person with a well-developed ego that enables him or her to delay gratification.

Emotional Tone.—This scale measures the degree of affective harmony within the psychic structure, and the extent to which fluctuation in the emotions as opposed to feelings that remain relatively stable is present. (Negative example: I feel tense most of the time. Positive example: Most of the time I am happy.) A low standard score shows poor affective control or great emotional fluctuation. A high standard score indicates that the adolescent has an ability to experience a range of many affects satisfactorily.

Body Image.—This scale indicates the extent to which the adolescent has adjusted to his or her body. (Negative example: In the past year, I have been very worried about my health. Positive example: The recent changes in my body have given me some satisfaction.) A low standard score shows continuing confusion about body boundaries or awkwardness about body changes that are occurring. A high standard score shows a well-structured body concept with well-defined body boundaries.

Social Relationships.—This scale assesses object relationships and friendship patterns. (Negative example: I usually feel out of place at parties and picnics. Positive example: Being together with other people gives me a good feeling.) A low standard score indicates that the adolescent has not developed good object relations and feels lonely and isolated. A high standard score shows a well-developed capacity for empathy.

Morals.—This scale measures the extent to which the conscience or superego has developed. (Negative example: I would not stop at anything if I felt I was done wrong. Positive example: I would not hurt someone just for the "heck of it.") A low standard score demonstrates a poorly developed superego. A high standard score signifies a well-developed sense of duty, responsibility, and concern for others.

Sexual Attitudes.—This scale concerns itself with the adolescent's feelings, attitudes, and behavior toward the opposite sex. (Negative example: The opposite sex finds me a bore. Positive example: I think that boys/girls find me attractive.) A low standard score demonstrates that the adolescent has a relatively conservative attitude toward sexuality. A high standard score means relative openness to sexuality.

Family Relationships.—This scale is concerned with how the adolescent feels about his or her parents and the kind of relationships he or she has with them. This scale also examines the emotional atmosphere in the home. (Negative example: Understanding my parents is beyond me. Positive example: I think that I will be a source of pride to my parents in the future.) A low standard score implies that the adolescent does not get along well with his or her parents and that tension exists in the home. A high standard score indicates that the adolescent communicates openly with his or her parents.

Mastery.—This scale assesses how well an adolescent adapts to his or her immediate environment. (Negative example: I am fearful of growing up. Positive example: When I decide to do something, I do it.) A low standard score shows an inability to finish tasks. A high standard score signifies a well-functioning adolescent who is able to deal with frustration.

Vocational-Educational Goals.—This scale measures how well the adolescent is faring in accomplishing the tasks of learning and planning for a vocational future. (Negative example: I feel that working is too much responsibility for me. Positive example: I am sure that I will be proud about my future profession.) A low standard score represents a failure on the part of the adolescent to work well within the school system and to make a reasonable plan for the future. A high standard score indicates an adolescent who works effectively within the educational system and who has made plans for the future.

Emotional Health (Previously Named Psychopathology).—This scale identifies emotional health that is the absence of severe psychopathology. (Negative example: I am confused most of the time. Positive example: Other people are not after me to take advantage of me.) A low standard score points to severe psychopathology on a clinical level. A high standard score indicates a relative lack of overt symptoms.

Superior Adjustment.—This scale measures how well the adolescent copes with himself or herself, other people, and his or her world. This scale could also be defined as a measure of ego strength. (Negative example: I do not like to put things in order and make sense of them. Positive example: Dealing with new intellectual subjects is a challenge for me.) A low standard score denotes that the adolescent does not deal adequately with his or her environment. A high standard score indicates a well-functioning coping system.

Idealism.—This scale measures an adolescent's ideals and his or her willingness to help others. (Negative example: I am against giving so much money to the poor. Positive example: I am going to devote my life to helping others.) A low standard score indicates that the adolescent is more concerned with himself or herself than others. A high standard score indicates that the adolescent is willing to help others and is concerned with social problems.

Subjects

The composition of our sample is shown in Table 1. (Please note that we did not plan our research to become a longitudinal study. It was a "sample of opportunity," ie, we collected the data separately. It was only in 1988 that we thought it might be interesting to compare these three different historical samples.)

Data were based on the responses of teenagers in three cohorts: (1) In the 1960s, 13- to 19-year-olds were drawn from two suburban high schools in the Chicago metropolitan area. One study focused on 16- to 19-year-olds of both sexes, while the other focused on 13- to 15-year-old males. Thus, only a small sample of 13- to 15-year-old girls was available in the 1960s cohort. (2) In the 1970s, subjects were drawn from high schools in the Chicago suburbs, rural areas in Minnesota and Nebraska, and a high school in Burlington, Vt. Subjects were also drawn from Roman Catholic parochial high schools in Chicago, and a private academy in Vermont. (3) In the 1980s, subjects were drawn from (a) the City of Baltimore, Md; (b) the Chicago suburbs; (c) Army dependents from Washington, DC; (d) Hawaii; and (e) New York City. There were 123 subjects for each of the four cells (young and old, male and female). Identical numbers were used for each of the four groups.

ANALYSES AND RESULTS

To test OSIQ scale differences across the decades, a three-way MANOVA was conducted. The three ways of classification were gender (male vs female), age (younger [13 to 15 years] vs older, [16 to 19 years]), and cohort (1960s, 1970s, and 1980s). The dependent variables were the OSIQ scale scores. The main effect of the cohort was found to be statistically significant ($F=29.9$; $df=22$; $P=.000$. Thus, ANOVAs were conducted separately on each OSIQ scale. All 11 scales showed a significant ($P<.01$) main effect for decade. One scale, body image, showed a significant gender-by-cohort effect. No other cohort interaction was significant ($F=24.6$; $df=2$; $P=.000$).

To explicate these results, let us examine the standard scores as represented in the profiles of the three adolescent groups: from the 1960s, from the 1970s, and from the 1980s (Figs 1 through 4). The gray area represents the norming group, which in this project was the 1970s adolescents. If we had used either of the other adolescent cohorts as the norming group, the results would have been the same.

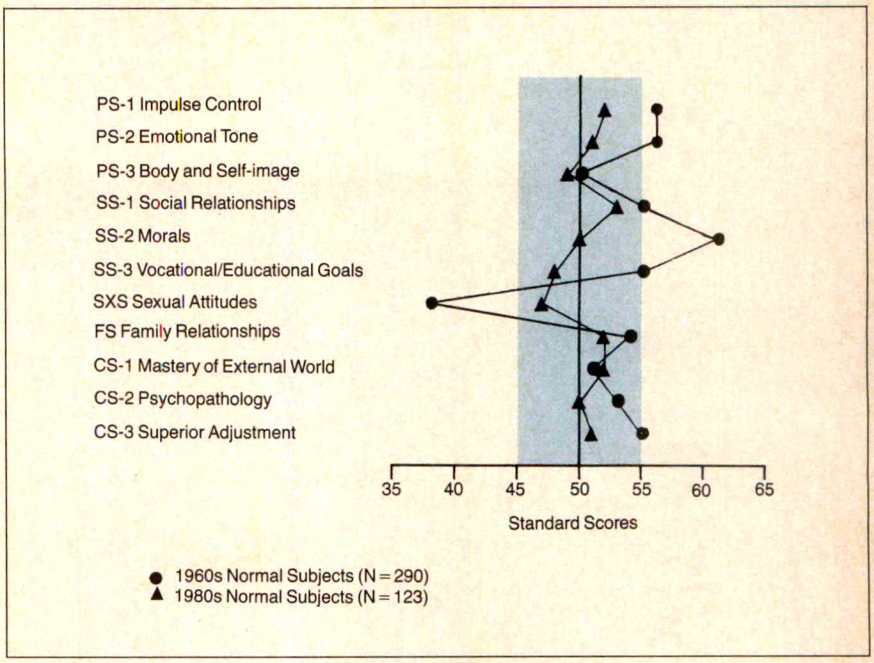


Fig 1.—Offer Self-Image Questionnaire profile comparison of normal adolescents (1960s vs 1980s) for younger males, aged 13 to 15 years. The higher the score, the better the adjustment in an area. In the psychopathology scale, the higher the score, the better the mental health.

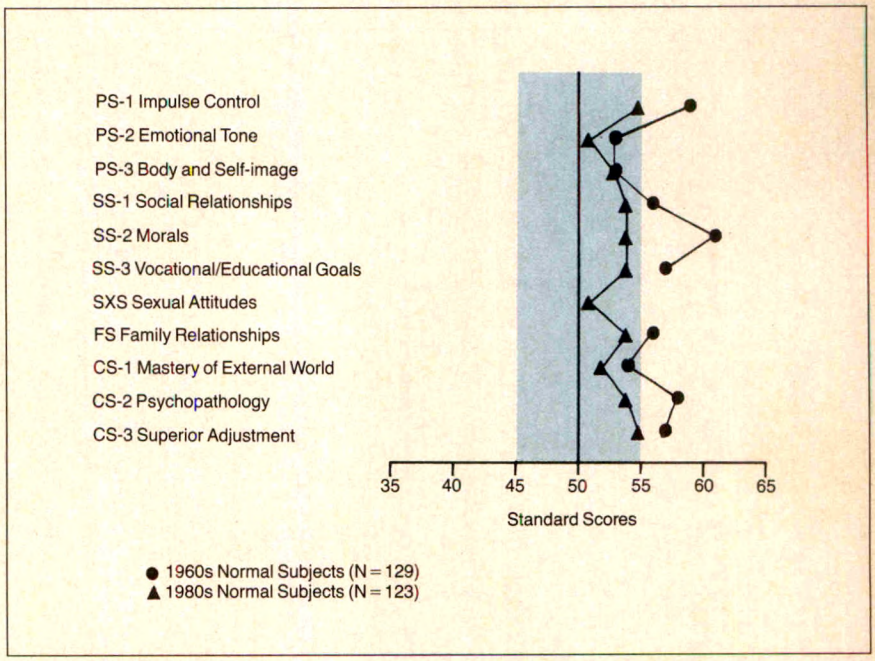


Fig 2.—Offer Self-Image Questionnaire profile comparison of normal adolescents (1960s vs 1980s) for older males, aged 16 to 19 years. The higher the score, the better the adjustment in an area. In the psychopathology scale, the higher the score, the better the mental health.

It is clear, from these profiles, that the adolescents from the 1960s had the overall best self-image, the adolescents from the 1970s had the overall worst self-image, and the adolescents from the 1980s were in-between. Regarding the body image gender-by-decade effect, the profiles show differences are concentrated among the girls. Girls in the 1960s reported a much better body image than did girls in the 1970s or the 1980s in-betweens. Boys showed almost no body image differences across the decades.

To explore differences at the item lev-

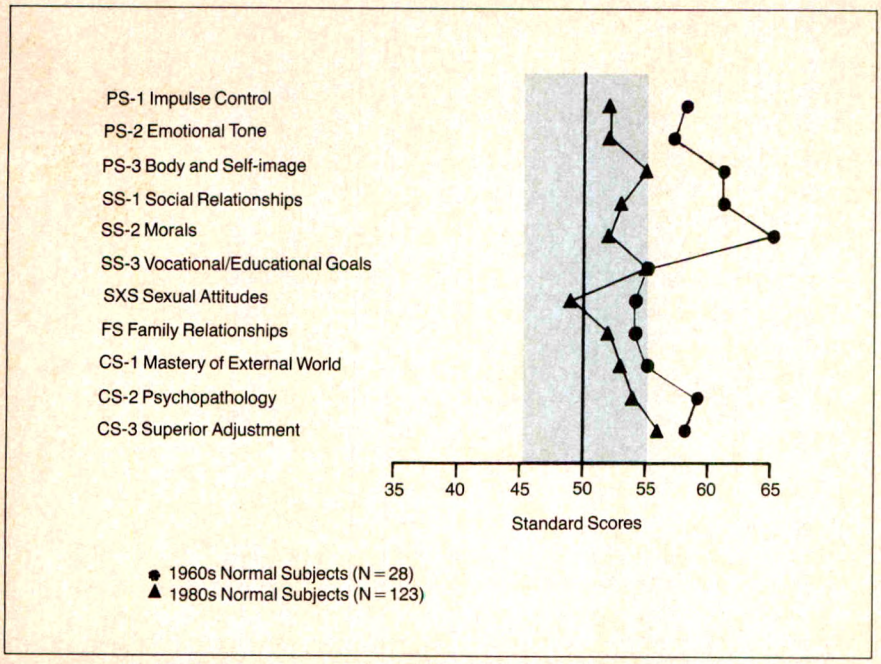


Fig 3.—Offer Self-Image Questionnaire profile comparison of normal adolescents (1960s vs 1980s) for younger females, aged 13 to 15 years. The higher the score, the better the adjustment in an area. In the psychopathology scale, the higher the score, the better the mental health.

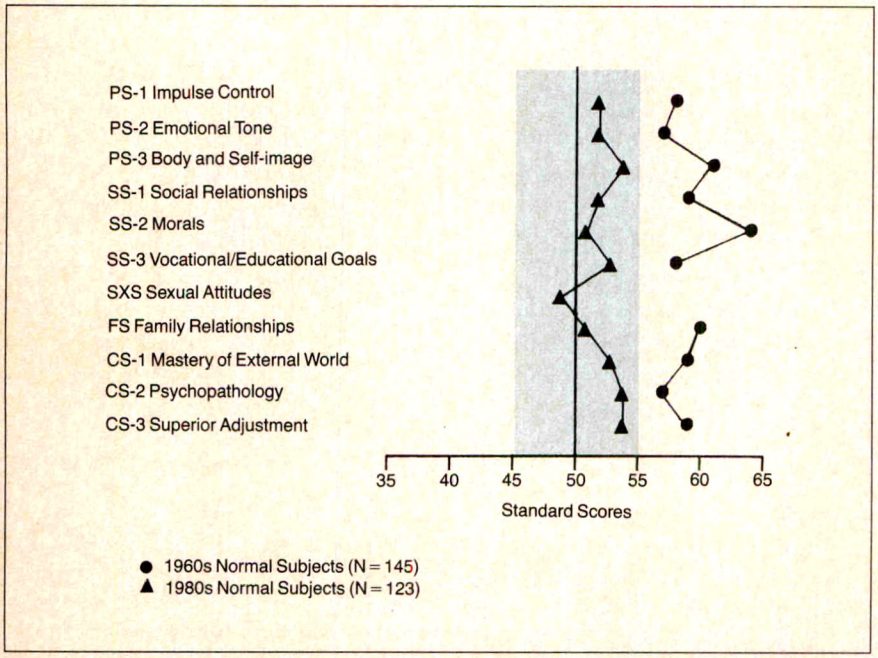


Fig 4.—Offer Self-Image Questionnaire profile comparison of normal adolescents (1960s vs 1980s) for older females, aged 16 to 19 years. The higher the score, the better the adjustment in an area. In the psychopathology scale, the higher the score, the better the mental health.

el, percent endorsements were examined for each item. An item was considered endorsed if a subject responded to it with a 1 (describes me very well), 2 (describes me well), or 3 (describes me fairly well). (There are six scale points for each item: the other scale points are 4 [does not quite describe me], 5 [does not describe me], and 6 [does not describe me at all].) An item was not considered endorsed if a subject responded to it with a 4 through 6 score). Percent endorsements for a certain item refer to the percentage of subjects in any particular subgroup endorsing that item. Percent endorsements were examined for four subgroups—young and older males, and young and older females—for each of the three decades. The items were examined with respect to whether they met the following criteria: (1) Endorsement had to follow a specific pattern across the decades for each of the four (age-gender) subgroups. This pattern was chosen based on the Easterlin population density theory.[15] National Center for Health Statistics[19] data were used to calculate the ratio of adolescents in the total US population. Our adolescent data were collected in 1963, 1975, and 1981. The density of adolescents was highest in 1975 (0.20), lowest in 1963 (0.12), and in-between in 1981 (0.17). To follow this pattern, in terms of the Easterlin theory, for each of the four subgroups item endorsement in the 1960s had to be the most healthy (either highest or lowest endorsement depending on the phrasing of the item) across the three decades studied, and 1970s endorsement had to be the least healthy. Endorsement had to be intermediate for the 1980s. (2) If percent endorsements did not show this pattern, they had to be consistent across the decades for each of the four subgroups. For each subgroup the pattern of percent endorsement had to be the same (eg, lowest in the 1960s, higher in the 1970s, and highest in the 1980s).

A separate analysis concerned items showing consistently extreme endorsement across the decades. Similarity was defined as extreme percent endorsement for all four subgroups—young male, young female, older male, older female—across the three decades. Items were chosen (1) when percent endorsements were 80% or more for 11 or more of the 12 cells (four subgroups across three decades) and the average percent endorsement in each decade was 90% or more, or (2) when percent endorsements were 20% or less for 11 or more of the 12 cells and the average percent endorsement in each decade was 10% or less.

Exploring the generation effect on the item level, we were interested to see which items showed the cohort effects (criterion 1) of the three decades (see Table 2).

Nine items were found to fit the crite-

Table 2.—Items Showing an Endorsement Pattern Across Three Decades Corresponding to a Cohort Effect*

Item No.	Item
Positive endorsement	
65.	I do not mind being corrected, since I can learn from it.
74.	For me good sportsmanship in school is as important as winning a game.
116.	Eye for an eye and tooth for a tooth does not apply for our society.
Negative endorsement	
8.	I "lose my head" easily.
50.	I get violent if I don't get my way.
61.	I often feel that I would rather die than go on living.
81.	I fear something constantly.
108.	When I enter a new room I have a strange and funny feeling.
114.	I do not enjoy solving difficult problems.

*The cohort effect predicts that larger adolescent cohorts will have poorer self-image than will smaller cohorts. This effect predicts that the 1970s cohort will show the poorest self-image and the 1960s the best self-image with the 1980s between the other two.

Table 3.—Items Showing Consistent Endorsement Across Three Decades*

Item No.	Item	%
High endorsement		
44.	I feel relaxed under normal circumstances.	91-92
58.	At times I think about what kind of work I will do in the future.	93-95
68.	I enjoy life.	90-93
70.	A job well done gives me pleasure.	97-99
79.	I feel that there is plenty I can learn from others.	93-97
83.	I like to help a friend whenever I can.	94-97
88.	Being together with other people gives me a good feeling.	93-94
123.	Usually I control myself.	90-93
Low endorsement		
14.	I feel that working is too much responsibility for me.	5-7
15.	My parents will be disappointed in me in the future.	6-7
20.	Only stupid people work.	1-3
25.	I do not like to put things in order and make sense of them.	9-10
48.	Telling the truth means nothing to me.	7-10
95.	My parents are ashamed of me.	4-7
97.	Thinking or talking about sex frightens me.	7-10

*Items were identified that showed extreme endorsement or negation: 80% or more endorsement or negation for at least 11 or 12 cells (younger/older/male/female across three decades) with endorsement or negation in each decade of 90% or more.

rion regarding a specific pattern of percent endorsement across the decades. These nine items indicate that adolescents in the 1960s had the most control of themselves, had the highest standard of morals, and most enjoyed coping with difficult problems, particularly as contrasted to the 1970s adolescents. The latter group had the lowest self-image in these areas; as ensured by the criterion, the 1980s adolescents were in-between. (Note: The probability of finding 9 items or more of 130 to have met this criterion was determined by ascertaining the probability of finding this pattern with respect to any 1 item and using the normal approximation to the binomial expansion to determine the probability of 9 or more such events of 130. Results showed that the probability of obtaining 9 such events was $P<.001$.)

Let us turn our attention to the areas where extremes of endorsement across the three decades existed (Table 3).

As we can see from Table 3, there were many areas of consensus among adolescents over the three decades, namely, self-feelings (such as enjoying life and being relaxed), values (such as affirming the worth of work), peer relationships, impulse control, problem solving, and relationships with parents.

NORMAL, OR MENTALLY HEALTHY, ADOLESCENTS

As we stated above, the overriding finding of our research over the years has been that statistically normal (ie, the majority of) adolescents function well. Results indicate that normal adolescents enjoy life and are happy with themselves most of the time. They do not have major problems with their body image or physical development. Sexuality is not a problem for them. When they compare themselves with other people, they do not feel inferior nor do they feel other people treat them adversely. Under normal circumstances they are relaxed. They believe they can deal with most ordinary life situations. More importantly, they have confidence that when presented with new and challenging situations, they will be able to cope with them.

One item, "A job well done gives me pleasure," has been highly endorsed since we started our first research in 1963; this high rate of endorsement shows the work ethic in its clearest form. Judging by the responses, this is a universal value of adolescents. The majority of teenagers are work oriented and state that they will be proud of their future profession. Although they may worry about their economic future, or, to put it differently, the job market, the majority do not want to be supported and will do their utmost to find an appropriate job.

The most important finding of our studies has been the way the adolescent feels about his or her family. Much has been written about issues like "the generation gap," or the "natural rebellion of adolescents against their parents." We have not found this to be the case. The majority of adolescents in our studies get along well with and do not perceive any major problems between themselves and their parents. They simply do not present any kind of evidence that a major intergenerational conflict exists. That does not mean they always get along with either one or both of their parents, but it does mean that the family serves as a first line of psychological defense for the teenagers. One consequence is that normality involves the teenager feeling good about his or her family, being proud of it, and liking it. Teenagers who feel this way have an advantage over adolescents who do not.

GENERATION DIFFERENCES

Our main hypothesis had to do with the finding that adolescents in the 1960s had a better self-image, in general, than those in the 1970s or 1980s. Adolescents in the 1980s had a better self-image than those in the 1970s, the latter having had the lowest self-image. The adolescents of the 1960s were least impulsive, had

the highest ethical values, had the best social and interpersonal relationships, were the least depressed, and were the least fearful about their future. The adolescents in the 1970s were worse off in each of these ways.

One way of explaining these findings has to do with the cohort theory, ie, the higher the ratio of adolescents in the total population, the more difficulties the adolescents have. They have more difficulty in obtaining jobs and in being admitted to good colleges. In general, there is more competition for everything that is available. This theory, which is called the "baby-boom–baby-bust theory," is based on two pioneer thinkers in that area. One is Easterlin,[15] whose book, *Birth and Fortune*, looked at the "baby-boom–baby-bust" hypothesis from an economic viewpoint and showed that the baby-boom generations, in general, had a harder time finding good jobs, economically were more deprived, and had a difficult time being successful. The other pioneer who has written on this topic in the past is Brenner,[20,21] who has shown that individuals in baby-boom generations suffer more from physical illness and also have more divorce and more breakdown in social networks. Based on that theory, the adolescents we studied in the 1960s were at the end of a baby-bust generation, those in the 1970s were in the middle of a baby-boom generation, and those in the 1980s were part of another baby-bust generation.

We did not find 1 item of the 130 that opposed our basic hypothesis that the adolescents from the 1960s had a better self-image than those in the 1970s or 1980s.

COMMENT

Diagnostic work with adolescents is difficult. Clinicians have a tendency to equate psychopathology with adolescence.[22] As we have demonstrated in this article, the majority of adolescents studied are well-adjusted and function within normal limits. We are aware that groups of adolescents not studied—for instance, high-school dropouts—might not be doing so well. Our data do not show systematic differences by social class or race.[18] In any event, among the adolescents studied there is a substantial minority (about 20%) whose importance should be underlined. Viewed nationally, that minority represents a large number of teenagers. In the United States, there are approximately 17 million adolescents. Our findings suggest that, at any one time, 20% or almost 3.5 million may require some kind of help or intervention. These adolescents are behaviorally and/or emotionally disturbed and are in need of the help of a health professional to overcome their problems. We found that sometimes these teenagers do not receive any help because it is thought by health professionals that all adolescents need to do is "grow out of adolescence" and into adulthood and their problems will be solved.

Disturbed adolescents do not necessarily "grow out of it." They need professional help. If they do not receive it, they only too often become disturbed young adults. Accuracy in diagnosis of disturbance as well as normality will result in better care for our adolescent population.

As a stage of life, adolescence has commonalities across all generations. Each cohort will face a slightly different world, but the size of the cohort by itself has an influence on psychosocial adjustment of adolescents. In addition, adolescents do not grow up in a vacuum. They are part of the total society and, hence, their development is influenced by economic, social, and political factors. We believe that it is crucial to understand individual adolescents as they grow up. Too often adults generalize about youth from afar—each group is unique. By the time we have begun to understand a particular cohort of adolescents, a new cohort has come along. The adolescents in this new cohort need to be studied to do it justice, ie, understand its specific hopes and despairs, strengths and weaknesses. In any event, it is empirical data that will clarify what is expectable and what is worrisome among the extent generation of adolescents.

This investigation was supported in part by the Adolescent Research Fund of the Center for the Study of Adolescence, Michael Reese Hospital and Medical Center, Chicago, Ill, and research grants from the Chicago Community Trust 1985-1988 (Dr Offer) and RO1MH42901 from the National Institute of Mental Health, Rockville, Md (Dr Howard).

References

1. Blos P. *On Adolescence*. New York, NY: Free Press; 1961.

2. Freud A. Adolescence. *Psychoanal Study Child*. 1958;13:255-278.

3. Hall GS. *Adolescence: Its Psychology and Its Relation to Physiology, Anthropology, Sociology, Sex, Crime, Religion and Education*. New York, NY: D Appleton Co; 1904.

4. Rabichow HG, Sklansky MA. *Effective Counseling of Adolescents*. Chicago, Ill: Follett; 1980.

5. Hechinger F, Hechinger G. *Teenage Tyranny*. New York, NY: William Morrow & Co; 1963.

6. Offer D, Ostrov E, Howard KI. Epidemiology of mental health and mental illness among adolescents. In: Call JD, Cohen RL, Harrison SI, Berlin IN, Stone LA, eds. *Basic Handbook of Child Psychiatry*. New York, NY: Basic Books Inc Publishers; 1987:chap 9.

7. Burnam NA, Hough RL, Escobar JI, et al. Six-month prevalence of specific psychiatric disorders among Mexican-American and non-Hispanic whites in Los Angeles. *Arch Gen Psychiatry*. 1987;44:687-694.

8. Canino GJ, Bird HR, Shrout PE, et al. The prevalence of specific psychiatric disorders in Puerto Rico. *Arch Gen Psychiatry*. 1987;44:727-735.

9. Karno M, Hough RL, Burnam A, et al. Lifetime prevalence of specific psychiatric disorders among Mexican-American and non-Hispanic whites in Los Angeles. *Arch Gen Psychiatry*. 1987;44:695-701.

10. Klerman GL, Weissman MM. An epidemiologic view of mental illness, mental health, and normality. In: Offer D, Sabshin M, eds. *Normality and the Life Cycle*. New York, NY: Basic Books Inc Publishers; 1984:315-344.

11. Uhlenhuth EH, Balter MB, Mellinger GD, Cisin IH, Clinthorne J. Symptom checklist syndromes in the general population: correlations with psychotherapeutic drug use. *Arch Gen Psychiatry*. 1983;40:1167-1173.

12. Holinger PC, Offer D, Ostrov E. Suicide and homicide in the United States: an epidemiological study of violent death, population change, and the potential for prediction. *Am J Psychiatry*. 1987;144:215-219.

13. Johnston LD, O'Malley PM, Bachman JG. *Drug Use Among American High School Students, College Students, and Other Young Adults: National Trends Through 1985*. Washington, DC: National Institute on Drug Abuse; 1986. US Dept of Health and Human Services publication ADM 86-1450.

14. Enright RD, Levy VM Jr, Harris D, Lapsley DK. Do economic conditions influence how theorists view adolescents? *J Youth Adolesc*. 1987;16:541-559.

15. Easterlin RA. *Birth and Fortune*. New York, NY: Basic Books Inc Publishers; 1980.

16. Holinger PC, Offer D, Zola M. A prediction model of suicide among youth. *J Nerv Ment Dis*. 1988;176:275-279.

17. Offer D, Ostrov E, Howard KI. *The Adolescent: A Psychological Self-Portrait*. New York, NY: Basic Books Inc Publishers, 1981.

18. Offer D, Ostrov E, Howard KI, Atkinson R. *The Teenage World: Adolescents' Self-Image in Ten Countries*. New York, NY: Plenum Press; 1988.

19. *National Center for Health Statistics: Advance Report, Final Mortality Statistics, 1982, Monthly Vital Statistics Report*. Hyattsville, Md: US Dept of Health and Human Services; 1984;33:9. Public Health Service publication 85-1120.

20. Brenner MH. *Time Series of Relationships Between Selected Economic and Social Indicators*. Springfield, Va: National Technical Information Service; 1971.

21. Brenner MH. Mortality and the national economy: a review, and the experience of England and Wales, 1936-76. *Lancet*. 1979;2:568-573.

22. Offer D, Ostrov E, Howard KI. The mental health professional's concept of the normal adolescent. *Arch Gen Psychiatry*. 1981;38:149-152.

Drug Errors and Incidents in a Neonatal Intensive Care Unit

A Quality Assurance Activity

Michael J. Vincer, MD, FRCPC; Joan M. Murray, RN; Anne Yuill; Alexander C. Allen, MD, FRCPC; Jacquelyn R. Evans, MD, FRCPC; Dora A. Stinson, MD, FRCPC

• We prospectively examined the causes of medication errors and incidents in a level 3 neonatal intensive care unit for a 2-year period. There were 313 incidents in 23 307 patient days (13.4 incidents per 1000 patient days). The relative risk of incidents was greater in more intensive levels of care. The two most common causes of incidents were neglecting to give a medication on schedule (n = 52) and nonregulation of an intravenous infusion (n = 32). Twenty percent of orders made by physicians that were in error resulted in serious incidents compared with only 6% of all other causes.

(*AJDC*. 1989;143:737-740)

Medication errors for patients in the hospital are an unfortunate cause of iatrogenic disease. Serious morbidity and even mortality has resulted from medication errors.[1,2] Various investigators have identified specific causes for errors, such as mistaken identity of drug vials,[2] errors in computation of dosage,[3,4] and errors in physician prescriptions.[5] To our knowledge, there has not yet been a prospective analysis of the causes of medication errors and incidents over an extended period in a neonatal intensive care unit.

As a quality assurance activity, we have established a regular audit of all medication errors and incidents in our neonatal intensive care unit with a view to establishing a cause for each incident. This audit began in late 1985 and is ongoing. The purpose of this study is to document our experience, with particular emphasis on the cause of all medication errors and incidents in a neonatal intensive care unit for the calendar years 1986 and 1987.

Accepted for publication December 12, 1988.

From the Department of Neonatal Pediatrics, Dalhousie University (Drs Vincer, Allen, Evans, and Stinson), and the Departments of Nursing (Ms Murray) and Pharmacy (Ms Yuill), Grace Maternity Hospital, Halifax, Canada.

Reprint requests to Department of Neonatal Pediatrics, Grace Maternity Hospital, 5821 University Ave, Halifax, Nova Scotia, Canada B3H 1W3 (Dr Vincer).

METHODS

The Special Neonatal Care Unit (SNCU) at Grace Maternity Hospital, Halifax, Canada, is a level 3, exclusively inborn nursery. Approximately 5500 newborns are delivered each year at the Grace Maternity Hospital, of which approximately 1200 are admitted to the SNCU. Grace Maternity Hospital is a university-affiliated teaching hospital with a large complement of house staff, including one neonatal fellow, one to two pediatric residents (generally at or under the second-year level of a 4-year program), one to two interns, five to eight fourth-year medical students, and five neonatal intensive care physicians (physicians with a provincial medical license to practice in a neonatal intensive care unit under the supervision of a neonatologist) at any time.

Drug distribution in the SNCU is based on a traditional system of nurses who review the drug orders made by physicians, prepare medication cards, mix drugs from the unit drug stock, and then finally administer the drug. There is one neonatal pharmacist who provides pharmacy support, one nursing unit coordinator responsible for nursing administrative needs, one head nurse, two assistant head nurses, approximately 75 full- or part-time nurses, and 4.25 neonatologists in the SNCU.

Medication incidents are either self-reported or reported by another individual who identified the incident. In 1985, efforts were made to reduce the punitive aspect of reporting these incidents and to utilize the educational value of these reports through nursing teaching sessions. This effort was associated with approximately a fourfold to sixfold annual increase in the reporting of medication incidents from 1985 onward compared with 1980 to 1984. In addition, the use of a medication "error" form was altered to a medication "incident" form for the following two reasons: (1) to reduce the emotional content of the report, and (2) to include those events that are not errors but that result in the incorrect administration of medications to patients (eg, an intravenous line that extravasates into the interstitium, leading to a late drug administration). A new report form was introduced that provided more information about each incident than previously available, particularly concerning the cause of the incident.

A committee of three, comprising a neonatologist (M.J.V.), the nursing unit coordinator (J.M.M.), and the clinical neonatal pharmacist (A.Y.), was formed to review medication incidents on a continuous basis. This committee's task was to review all medication incidents and assign each to one of the following four categories: (1) human error—an error that health care workers make in the process of administering medications, (2) mechanical failure—a breakdown in the equipment providing support for medication administration, (3) other events—events that can be expected to occur in the normal operation of a neonatal intensive care unit, and (4) unknown. The committee placed a great deal of emphasis on assigning a specific cause to each incident in anticipation that this would be the best type of information for designing corrective measures. The effect of the incident for the patient was also recorded (eg, overdose or late medication). When the data were collected, they were abstracted onto a medication incident abstract and entered into a computer for later analysis.

DEFINITION OF MEDICATION INCIDENTS

Violating the standards for correctly administrating medications in the SNCU required an incident form to be filled out. Therefore, the following definitions of medication incidents were used.

1. *Wrong time.*—Medications were not given within 30 minutes of the scheduled time.

2. *Dosing errors.*—Drug dosage was more than 10% over or under the ordered dose (regardless of medication), or for intravenous infusions, a 24-hour volume of more than 10% over or under the ordered rate, or an hourly rate of more than 50% over or under that required.

3. *Wrong drug.*—Incorrect drug was administered except for generic substitution.

4. *Outdated medication.*—Intravenous solutions or parenteral nutrition was not changed within 24 hours or drugs had an

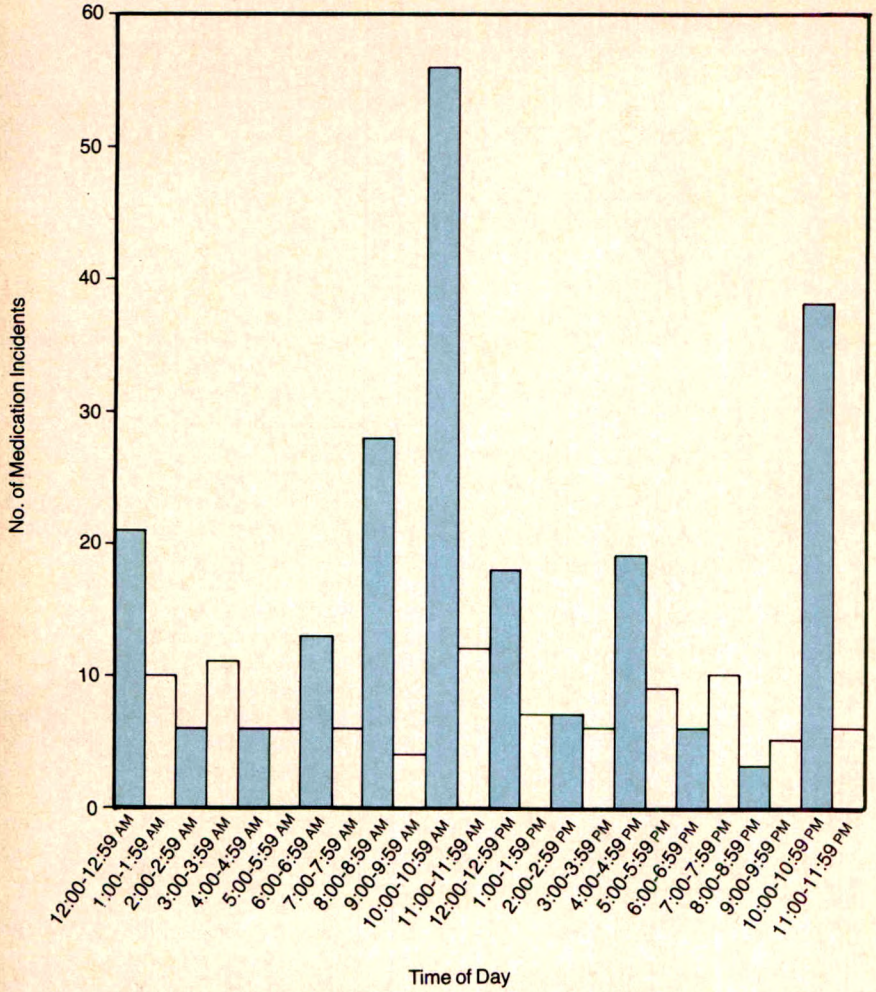


Fig 1.—Number of medication incidents (1986-1987) over the 24-hour period.

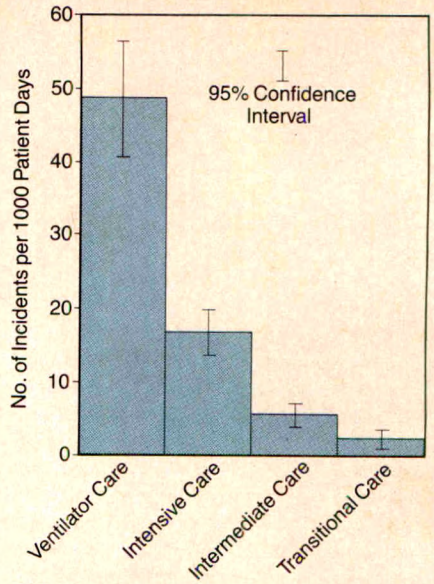
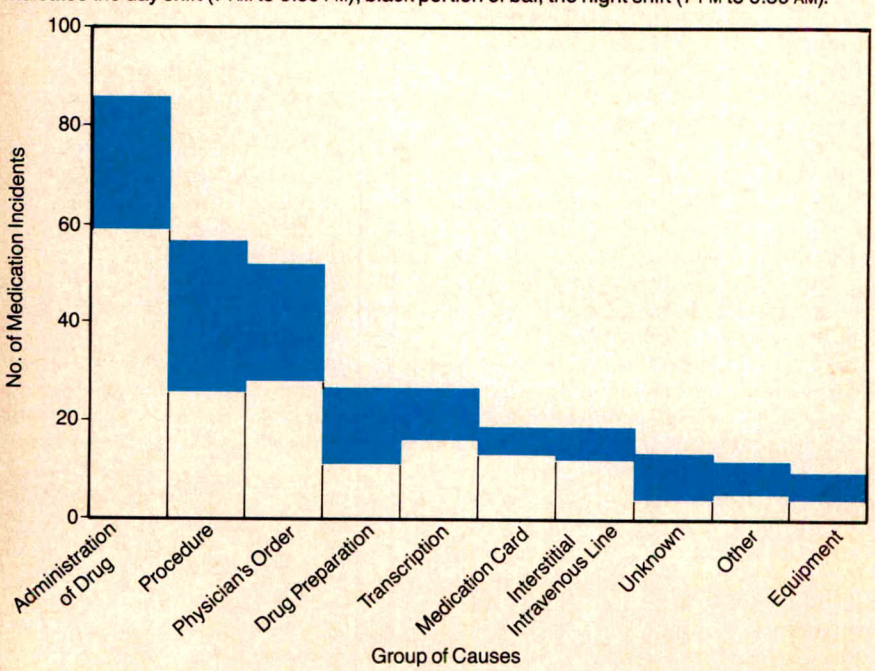


Fig 2.—Relative risk of medication incidents (number of incidents per 1000 patient days) for those receiving ventilator, intensive (non-ventilator), intermediate, and transitional care.

Fig 3.—Number of medication incidents vs the 10 major groups of causes. White portion of bar indicates the day shift (7 AM to 6:59 PM); black portion of bar, the night shift (7 PM to 6:59 AM).



expired manufacturer's date before administration.

5. *Contraindicated solution combinations.*—Incompatible combinations of agents were given in an intravenous solution (eg, sodium bicarbonate and calcium gluconate).

6. *Wrong dilution.*—An incorrect drug dilution mixture with the correct dosage was given to the patient.

7. *Wrong patient.*—Drug was given to the wrong patient.

8. *Omission.*—A scheduled dose was omitted.

9. *Extra dose.*—An extra dose was given.

10. *Unordered medication.*—An unordered medication was administered.

11. *Incorrect route.*—Drugs were given by an incorrect route.

12. *Interstitial intravenous line.*—Intravenous solutions extravasated into the interstitium, resulting in a slough of skin or a large area of edema.

RESULTS

For the period beginning January 1, 1986, through December 31, 1987, a total of 313 medication incidents were reported to the committee. During this time, there were 23 307 patient days in the SNCU, giving a relative risk of 13.4 incidents per 1000 patient days. Approximately 50 000 drug doses or intravenous infusions were administered each year.

Under normal circumstances, the

first dose of a scheduled drug is given when ordered. Subsequent doses are given according to the following routine: (1) once daily at 10 AM; (2) twice daily at 10 AM and 10 PM; (3) three times daily at 8 AM, 4 PM, and midnight; (4) four times daily at 10 AM, 4 PM, 10 PM, and 4 AM; and (5) six times daily at 10 AM, 2 PM, 10 PM, and 2 AM, and 6 AM. When analyzed by hour of occurrence, medication incidents occurred at six distinct 1-hour peaks at midnight, 8 AM, 10 AM, noon, 4 PM, and 10 PM (Fig 1). These peaks may be expected because of the nursery routine; however, it is unclear at this point if there is a higher rate of incidents at these times (ie, number of incidents per drug administered) because of insufficient data on the time of administration of all drugs in the SNCU.

Not surprisingly, the relative risk (the number of incidents per number of patient days) of medication incidents increased with increasing levels of newborn care (Fig 2). With a simple confidence interval for the difference between two independent proportions, the relative risk of a medication incident in patients receiving ventilator care (48.6 of 1000 patient days) was significantly greater ($P<.01$) than in those receiving nonventilator intensive care (16.8 of 1000 patient days), intermediate care (5.6 of 1000 patient days), or transitional care (2.3 of 1000 patient days).

The types of medication incidents are given in Table 1. Human error represents the largest group of incidents (86.6%), while mechanical failure, other events, and unknown categories combined account for only 13.4% of the incidents. Table 1 also shows that there were more day shift incidents reported (178/313 [57%]) than night shift incidents (135/313 [43%]). The nursing shifts in the SNCU are 12 hours long and start at 7 AM for the day shift and 7 PM for the night shift. Unfortunately, because the number of medications administered during each hour is unknown, data were insufficient to determine if there were proportionally more incidents occurring during the day shift than occurring during the night shift.

Ten major groups of causes of medication incidents could be identified (Fig 3). The two most frequent groups included problems attributed to the drug administration and failure to follow correct procedures (usually with infusion pumps). To be more specific, as shown in Table 2, the two most frequent causes of medication incidents were neglecting to give a drug at the scheduled time (16.6%) and failing to regulate an intravenous infusion properly (12.8%). Errors in the orders made by physicians tended to result in more serious incidents, 20% compared with only 6% of all other causes ($P<.001$, simple confidence interval for the difference between two independent proportions). Serious incidents were defined as those resulting in patient morbidity or a potential for morbidity.

Finally, the results of the medication incidents are noted in Fig 4. Errors in

Table 1.—Category of Error

Category	Day Shift	Night Shift	Total
Human error	157	117	**274**
Mechanical failure	4	4	**8**
Other events	15	9	**24**
Unknown	2	5	**7**
Total	**178**	**135**	**313**

Table 2.—Causes of Medication Errors

Causes	No. of Incidents
Incorrect administration of the drug	**84**
Neglect to give drug at scheduled time	52
Unaware drug order existed	13
Correct time for administration not identified	7
Wrong patient identified	4
Unaware drug already given	3
Medication given without an order	2
Correct route not identified	2
Medication not charted as given	1
Standard nursery procedures not followed	**56**
Intravenous drip not properly regulated	32
Miscellaneous procedural error	19
Incorrect operation of mechanical device	5
Physician's orders incorrect	**51**
An error in the order (eg, physician ordered an overdose)	25
Order not written according to nursery guidelines	12
Order written after it should have been ordered (based on clinical condition)	6
Verbal order	6
Ambiguous order	2
Faulty drug preparation	**26**
Wrong medication taken from shelf	16
Dose calculated incorrectly	6
Preparer unaware of correct dose	3
Drug dilution miscalculated	1
Error in transcription of physician's order	**26**
Transcribed incorrectly onto medication cards	11
Order misinterpreted	8
Order missed during transcription	7
Interstitial intravenous line	**18**
Problem with medication cards	**18**
Medication card is missing	5
Medication card misinterpreted	5
Medication card is in the wrong time slot	3
Medication card not cancelled with physician's order to discontinue drug	3
Failed to use medication card as a reminder of drug administration	2
Unknown	**13**
Other	**12**
Miscellaneous	8
Multifactorial	3
Patient unavailable	1
Equipment problems	**9**
Mechanical device failed to function correctly	5
Manufacturing defect	3
Equipment used inappropriately	1

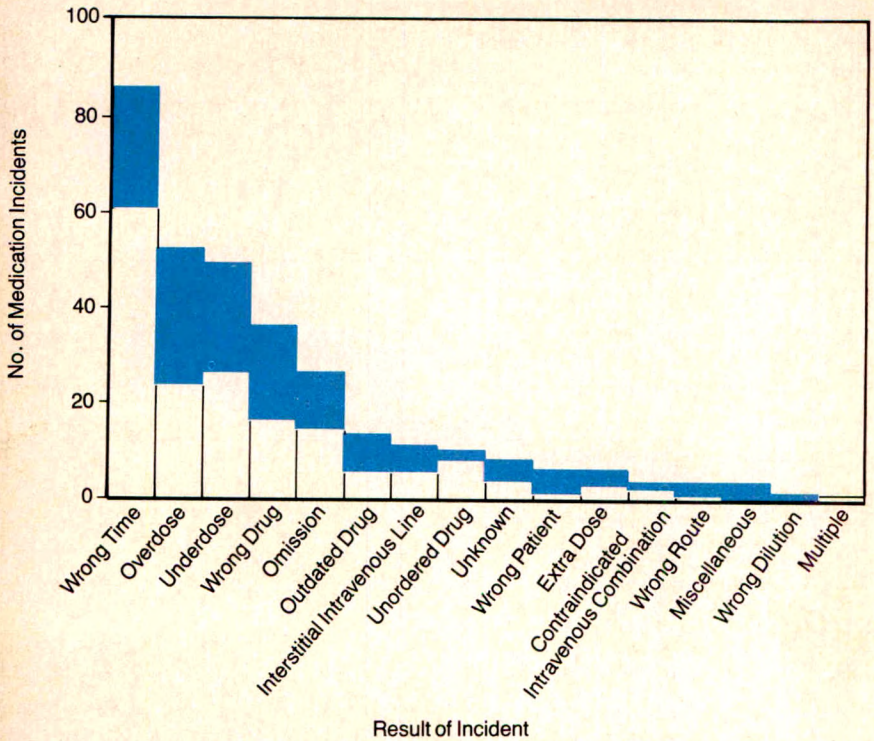


Fig 4.—Number of medication incidents vs result to the patient. White portion of bar indicates the day shift (7 AM to 6:59 PM); black portion of bar, the night shift (7 PM to 6:59 AM).

time (27.2%) and errors in dosage (32.2%) represent the majority of the incidents.

COMMENT

To our knowledge, this is the first attempt at identifying a specific cause for each medication incident in a neonatal intensive care unit. Although it requires far more time to identify the cause, the benefits are substantial. For example, many possible causes of dosing errors require very different corrective action. One of the most common causes of dosing errors in our nursery is the failure to regulate an intravenous infusion adequately, which is partly because of the use of infusion pumps that are outdated. These pumps do not have alarms if the intravenous tubing is inadvertently clamped or if the pump is not reset to the correct infusion rate after the tubing is purged. We used these medication incident reports as part of the justification to purchase better infusion pumps with appropriate alarms.

We attempted to review the process of drug distribution as recommended by the Canadian Society of Hospital Pharmacists[6]; however, we found that the resources required for such a process are far greater than presently available. With increased resources, we could better define the epidemiology of these incidents by having a daily profile of when drugs are given, having an audit of drug orders, and using the disguised observer technique to see if we were missing other incidents.[7] When resources are made available, much can be accomplished regarding prevention of errors, as suggested by Folli et al,[8] who showed that errors in orders made by physicians occurred at a rate of 4.7 per 1000 medication orders. In their study, a pharmacist regularly reviewed all physicians' orders and identified for the prescribing physician any errors before drug administration. They noted that physicians with the least training made the greatest proportion of errors.

In the past, physicians have not participated in a regular audit of medication incidents, and, therefore, prevention of morbidity and occasionally mortality of this iatrogenic disease has continued without their input. This process tends to be administrative, a role for which most physicians have had little preparation during their medical education. Nevertheless, our experience over the last 2 years with a physician member of the review committee has been positive. More physicians in our institution are now familiar with the process of medication distribution and administration, which has facilitated the dissemination of some constructive advice regarding prevention of medication incidents. This dissemination is particularly important since physicians' orders more frequently result in serious errors (20%) compared with all other causes (6%). Specifically, the three most serious errors in this study—an overdose of dopamine of four times the appropriate amount, an underdose of dopamine of 50%, and an overdose of prostaglandin E of 10 times the appropriate amount—were all caused by verbal orders that differed from the subsequently written order. These incidents provided support for the establishment of a policy for insisting on a written order before medication administration except in extreme emergencies.

CONCLUSION

The reporting of medication incidents by cause of incident in addition to the result to the patient is the most important point of the data presented. By understanding the causes of these incidents, it becomes possible to take specific action to prevent this source of iatrogenic disease.

References

1. Hoddinott BC, Gowdey CW, Coulter WK, Parker JM. Drug reactions and errors in administration on a medical ward. *Can Med Assoc J.* 1967;97:1001-1006.

2. Solomon SL, Wallace EM, Ford-Jones EL, et al. Medication errors with inhalant epinephrine mimicking an epidemic of neonatal sepsis. *N Engl J Med.* 1984;310:166-170.

3. Perlstein PH, Callison C, White M, Barnes B, Edwards NK. Errors in drug computations during newborn intensive care. *AJDC.* 1979;133:376-379.

4. Koren G, Barzilay Z, Modan M. Errors in computing drug doses. *Can Med Assoc J.* 1983; 129:721-723.

5. Grimwood K, Cook JJ, Abbott GD. Antimicrobial prescribing errors in children. *NZ Med J.* 1983;96:785-787.

6. Canadian Society of Hospital Pharmacists Standards Committee. CSHP guidelines for medication incident and medication discrepancy reporting in Canadian Hospitals. *Can J Hosp Pharmacol.* 1986;39:67-69.

7. Barker KN. The effects of an experimental medication system on medication errors and costs, part I: introduction and errors study. *Am J Hosp Pharmacol.* 1969;26:324-333.

8. Folli HL, Poole RL, Benitz HE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. *Pediatrics.* 1987;79:718-722.

Barriers to Bicycle Helmet Use Among Children

Results of Focus Groups With Fourth, Fifth, and Sixth Graders

Jonathan Howland, PhD, MPH; James Sargent, MD; Michael Weitzman, MD;
Thomas Mangione, PhD; Robert Ebert, PhD; Marianne Mauceri, RN; Marie Bond, EdM

• As a preliminary step in the development of a school-based educational intervention to promote bicycle helmet use among children, focus group encounters were conducted with fourth, fifth, and sixth graders at three elementary schools in the Boston, Mass, area. Analysis of transcripts of encounter tape recordings indicated that (1) the prevalence of helmet ownership and use was low, (2) children were concerned that helmet use would invite derision from their peers, and (3) children tended to respect other children who wore helmets. We concluded that focus groups can be useful in conceptualizing health education interventions and suggest that school-based peer-led bicycle helmet programs may be effective in developing normative change toward helmet use among elementary schoolchildren.
(*AJDC*. 1989;143:741-744)

The focus group is a qualitative technique for gathering information about consumers' perceptions and attitudes concerning specific products. Traditionally, focus groups have been used by private companies as an initial step in product development, or for the design of a promotional effort to enhance the marketing of an existing product. Recently, focus groups have also been used to inform the planning and implementation of public health campaigns.[1] Basch[2] has provided a comprehensive discussion of the application of focus groups in this context. Our article reports on the use of focus groups in the development of an intervention program for increasing bicycle helmet use among primary schoolchildren. To our knowledge, this is the first report on the use of focus groups for planning a health intervention with children in the elementary school grades.

Children are at risk for serious head injury resulting from bicycle crashes. Based on data developed by the National Electronic Injury Surveillance System, it is estimated that in 1985 there were approximately 574 000 bicycle injuries treated in emergency departments in the United States.[3] Half of these injuries occurred in children between the ages of 5 and 15 years; one third of these injuries involved the head, neck, or face. Approximately 600 children under the age of 15 years die each year in bicycle-related crashes.[4] Over 80% of these deaths involve trauma to the head.[2]

There is persuasive evidence that the risk of head injury can be effectively reduced through the use of safety helmets.[5-8] Nevertheless, children rarely wear helmets. Several studies suggest that the prevalence of bicycle helmet use among children is less than 5%.[4,9] As a result of a survey mailed to parents, DiGuiseppi and coworkers[10] found that 22.9% of third graders who owned bicycles and attended Seattle public schools owned helmets after a helmet promotion campaign in that city. This estimate, however, may be inflated by selection bias due to the small (48%) survey response rate.

The reasons for the low prevalence of helmet use among children are unclear, and there is little in the published literature to illuminate this question. We conducted focus group encounters with fourth-, fifth-, and sixth-grade students at three elementary schools in the Boston, Mass, area in the spring of 1988. Our purpose was to better understand barriers to helmet use among children aged 10 to 14 years as a first step in developing interventions to promote bicycle helmet use in this age group. We were interested in children's perceptions of the risks of bicycle-related head injury, their assessment of the potential seriousness of head injury, their knowledge of bicycle helmets and of helmet efficacy, and their attitudes toward helmet use by themselves and by others.

SUBJECTS AND METHODS
Selection of Subjects

A convenience sample of three schools was selected on the basis of the investigators' prior contacts and associations. One school (A) was a public elementary school located in an affluent semirural community approximately 60 miles from Boston; another was a private primary school (B) located in suburban New Bedford, Mass; and the third school was a public elementary school located in a racially mixed, inner-city Boston neighborhood (C).

School principals were contacted and informed of the purpose of the study. Principals selected a fourth-, fifth-, or sixth-grade class to participate. Classroom teachers were asked by the principals to choose 10 to 15 bicycle-riding students (an equal number of boys and girls) and request cooperation in a group discussion about bicycle helmets. Teachers were informed that any child expressing reluctance was to be excused from participation. Children willing to participate were given an informed consent form (approved by the Boston University School of Medicine Institutional Review Board) addressed to parents. The informed consent

Accepted for publication January 28, 1989.
From the School of Public Health (Drs Howland and Ebert) and the Department of Pediatrics (Drs Sargent and Weitzman), Boston University School of Medicine; the Center for Survey Research, Boston City Hospital, University of Massachusetts, Boston (Dr Mangione); the Greater New Bedford (Mass) Community Health Center (Ms Mauceri); and Childhood Injury Prevention Program, Department of Health and Hospital, Boston, Mass (Ms Bond).
Presented at the 116th Annual Meeting of the American Public Health Association, Boston, Mass, November 15, 1988.
Reprint requests to School of Public Health, Boston University School of Medicine, 85 E Newton St, Boston, MA 02118 (Dr Howland).

form described the study's purpose and procedures. Only children returning a consent form signed by parents were eligible to participate.

Focus Group Protocol

Focus groups were conducted by a nurse health educator (M.M.) with experience in conducting school-based risk modification programs. Each grade met separately for approximately 1 hour during school hours. Discussants sat at a table set up in a room designated by the school principal. Nonparticipating students were not allowed access for the duration of the focus groups. A script, in the form of a list of issues to be covered, was used to guide the discussion. The nurse educator was instructed, however, to use the script only for the purpose of facilitating discussion (ie, ongoing discussions were not interrupted to adhere to the script).[11] All encounters were tape-recorded using high-quality equipment, including several directional microphones.[11] Recorders were operated by a member of the study team. In addition, a psychologist (R.E.) observed the discussions and took notes on children's verbal and nonverbal behaviors. No props were used except a display of various types of helmets, which, at a specified time, children were encouraged to try on and discuss.

After the discussion children were informed that they would be given a gratuity in appreciation for their cooperation. Children were individually offered a choice between a new bicycle helmet or $5 cash (school A) or an $8 gift certificate redeemable at a regional record store chain (schools B and C). The dollar value of each option (helmets retailed for around $60) was stated. Student choices were recorded.

Data Analysis

After the focus group encounters, two of the investigators (J.H. and J.S.) listened to the tape recordings and reviewed the psychologist's notes. Each independently prepared a list of major discussion topics. The two lists were subsequently merged. One invesigator (J.S.) then listened to the recordings again, noting, as he listened, the frequency and/or degree of apparent consensus of responses to each discussion topic. Responses were ranked according to the following three-point scale: (1) frequent/high consensus, (2) frequent/divided opinion, and (3) infrequent. Representative responses for each discussion topic and for each response category were then culled for incorporation in this report.[11] Because results from the six focus groups were relatively consistent across gender, grade, and school, we pooled responses for analysis.

RESULTS

No children were excluded from participation by their parents. In all, 42 students participated in the study—22 fourth graders, 7 fifth graders, and 13 sixth graders. All students owned bicycles and used them regularly with the exception of one student whose bicycle was in disrepair. Five of the students (12%) owned bicycle helmets. All students had seen someone wearing a helmet while riding a bicycle.

When asked about their perception of bicycle injury severity, "What is the worst thing you can imagine happening to you if you crash your bike?", the most frequent responses were "cuts and scrapes" and "injury to arms and legs." Less frequently cited were injuries to the "head and neck" or "becoming paralyzed."

Only a few students associated bicycle crashes with dying. When students were asked a question specifically focused on head injury, "What could happen to you if you injured your head in a bike crash?", the most frequent responses were "concussion," "coma," "paralysis," and "getting knocked unconscious." When students were asked about their attitudes toward others wearing helmets, "How do you think someone looks when they are wearing a bike helmet?", the most frequent responses were positive: "smart," "safe," or "good." Or, "I'd think the person is protecting himself," "I'd think they're smart because if they are riding on a busy street and a car comes around the corner and doesn't see them then they can really hurt their head," and "I would think that is the kind of family that cares about safety and stuff." A number of students expressed indifference: "ordinary," "usual," or "no big deal." A minority of students had negative responses, such as "stupid," "retarded," or "different."

Several students distinguished between their attitudes toward wearing a helmet for sport or racing, as opposed to more routine bicycle riding, and gave the following replies: "When you look at a person who's doing it for sport or exercise then you think it is regular. But, if you see someone just going along you say, 'Geez, why is he wearing a helmet?'" "If you see someone on a ten-speed or a regular bike, riding along, it seems that you see an adult with a helmet more than a kid with one." "If they're riding a ten-speed and wearing a bike shirt you know that they're probably on a long-distance trip and wearing it [the helmet] for protection. But, if you see someone just riding around on a dirt bike wearing a helmet you think, 'Boy, that guy's mom must be all over him.'" "Looks [helmet] OK on a racer."

Style and design seemed important in determining students' attitudes toward helmet use by others: "Depends on the color." "It depends on what kind of helmet they're wearing, something just plastic...but if they're wearing a really bright helmet, that's different." "If someone comes in wearing a really nice, expensive, gorgeous helmet like those really expensive black slick teardrop ones you see in the movies...people would say 'That's cool!'"

In contrast to attitudes toward others and when asked the following question about their attitudes toward wearing a helmet themselves: "How would you feel about wearing a bike helmet?", few of the students expressed positive feelings about wearing helmets. The most frequent responses were "embarrassed," "stupid," "not cool," and "not tough." When asked how they would be perceived by their peers if they (the students) wore helmets, "What would your friends think if they saw you wearing a helmet?", tension was induced in the groups as indicated by increased laughter, talk among the students, and demonstrable responses: "They'd probably laugh at me." "They would call me a big sissy." "They would say I'm not tough." "Call me ugly and stupid." "Think I'm a weirdo." "Well, some people would laugh, and some people would call me names, but some people wouldn't say anything."

Very few students expressed indifference about others' attitudes: "If I wore a helmet and the kids laughed at me I wouldn't really care because I want to be safe riding my bike. I want to be protected and if they don't wear one and they get hit they can get a concussion." "If you're wearing your helmet and if they wipe out and get hurt they'll learn a lesson and not criticize people."

A few students owned helmets but had ceased using them. An account by one of the students is illustrative: "I got

it [the helmet] right after my [bicycle] accident and I wore it for a year and a half, basically because I was scared. It took me a while to just hop on my bike and start riding again because I was freaked out! My uncle got me the helmet because he was in a bike accident too. It was red to match my bike, and for a while I was kind of proud to wear it. It was like, 'See me, I got this!' But after a while people started giving me strange looks—not making fun of me—and asking, 'Why are you wearing that?' I used to just put it on anyway. Then, I would sneak it off and just hang it around my handlebars. After a while I just didn't wear it at all."

Finally, students were asked whether they thought there should be a law that required helmet use while riding bicycles. The most frequent responses suggested compliance: "I would wear one." "It wouldn't be different because you'd all be wearing it." "Nobody could laugh at you because you could laugh at them because they'd be wearing one too." "I wouldn't care because then everybody would have to wear one." "There should be a law. Nobody would laugh then."

There was not, however, consensus on this issue. Less frequent responses were: "Yeah, but not everybody wears seat belt." "There shouldn't be such a law." "I would protest." "It would be hard to get a law passed."

When children were asked to try on the demonstration helmets to see if they could find one they liked, all participated with interest and enthusiasm. Almost all identified a helmet they liked. One student said that she could not find one she liked. Color appeared to be an important determinant of helmet preference; black was most frequently selected, and white was least frequently chosen. Students were also partial to helmet design and styling; helmets with hard plastic shells were preferred over soft-shell models by boys, while girls were appreciative of the opportunity for variety provided by the interchangeable fabric covers of the soft-shell models.

When offered a choice between a helmet or an alternative gratuity for participation, 86% (36/42) chose helmets. Two students chose the alternative (an $8 gift certificate redeemable at a record store or $5 cash) because they already owned helmets. Four students not choosing helmets were fourth-grade boys at one school. One of these initially selected a helmet but the other three boys repeatedly insisted that he take the money instead. Finally, he relented.

COMMENT

Focus groups are by nature exploratory. It would be inappropriate to consider information thus gathered as representative of nonparticipating populations. For example, 12% of the participants in our focus groups owned helmets. This relatively high proportion perhaps reflects some bias in the way participants were selected (ie, teachers tended to select children known to use helmets). Furthermore, the circumstances of focus groups are such that the opinions of a few can have disproportionate impact on observers because participants differ with respect to willingness or comfort in expressing opinions in public and because of variation in effectiveness of communication. Focus groups can, however, provide a practical and inexpensive means for identifying issues, or the strength of issues, which might not have occurred to investigators. Accordingly, the information derived from focus groups can provide valuable insights into attitudes and behaviors in addition to informing the formative stage of more rigorous research.

Strict protocols for focus groups exclude discussions among participants who know one another.[11,12] The rationale for this is that free expression of opinions and feeling might be constrained when discussants have prior knowledge of each others' views on the issues under consideration.[11] Moreover, focus groups are usually limited to adults because children, and particularly adolescents, may be less forthcoming in the presence of adults.[11] Despite our deviation from these rules, we believe our experience with focus groups involving elementary schoolchildren was instructive. We were impressed by the willingness to cooperate demonstrated by the participating children. Students seemed to both acknowledge the topic as serious and enjoy the opportunity to express their opinions. Some students were more vocal or articulate than others; however, when expression was elicited by the focus group leader the more reserved students appeared to participate without inhibition. Thus, we concluded that focus groups can be successfully and effectively conducted among children at elementary school grade levels as low as the fourth grade.

Distinct patterns emerged from the six encounters we conducted: children were aware of the risks associated with bicycle riding, but they were not particularly concerned with these risks in the context of everyday riding; the prevalence of helmet ownership and use was low, as we anticipated; use of helmets was perceived as acceptable for certain kinds of bicycle riding (racing or touring), but less appropriate for routine riding; helmet color and design were important (ie, helmets were viewed in the context of dress); and children perceived helmets as functional in protecting against head injury, but feared being teased or derided by their peers for wearing helmets. Perhaps the most significant findings were that children did not hold negative attitudes toward other children who wear helmets and that children were not resistant to the idea of mandatory helmet use. These findings were consistent with the results of a similar study of secondary school students in Australia.[13] Together, the Australian findings and our own suggest that an intervention program to promote helmet use should focus on changing children's perceptions of how they might be viewed by their peers; children need to be reassured that their peers consider wearing helmets "smart."

Parents undoubtedly play an important role in children's ownership and use of bicycle helmets. We did not direct discussion toward parental attitudes because we wanted to maintain focus on how children perceived helmets. Nevertheless, in designing educational interventions, parents' perceptions and attitudes should be addressed. Focus groups with parents might facilitate the development of strategies aimed at convincing parents of the benefits of helmet use for their children.

In conclusion, we believe that (1) focus group encounters can play an important role in the planning and implementation of public health programs, (2) focus groups can be effectively conducted with school-age chil-

dren if the topics of discussion are relevant to their routine behaviors, and (3) misperceptions of peer attitudes appear to be a major barrier to helmet use among school-age children. These findings suggest that interventions, whether organized promotion programs or individual guidance by parents, teachers, or pediatricians, should focus on assuring children that helmet use is accepted by their peers.

This study was supported by Boston University School of Public Health Basic Research Support Grant 57-244-1108-5.

The authors wish to thank the following helmet manufacturers for donating bicycle helmets to this study: Bell Helmets Inc; Giro Sports Design Inc, Santa Cruz, Calif; Pro-Tec Inc, Bellevue, Wash; and Vector Products, Seattle, Wash.

References

1. Simmons J, Howland J, Brent P, Roberts E. Using focus groups for developing educational interventions for patients with chronic obstructive airway disease. Presented at the Annual Meeting of the American Public Health Association; November 3, 1981; Los Angeles, Calif.

2. Basch CE. Focus group interview: an underutilized research technique for improving theory and practice in health education. *Health Educ Q.* 1987;14:411-448.

3. Centers for Disease Control. Bicycle-related injuries: data from the national electronic injury surveillance system. *MMWR.* 1987;36:269-270.

4. Weiss BD. Bicycle helmet use by children: knowledge and behavior of physicians. *Am J Public Health.* 1986;76:1022-1023.

5. Dorsch MM, Woodward AJ, Somers RL. Do bicycle helmets reduce head injury severity in crashes? *Accid Anal Prev.* 1987;9:183-190.

6. Wood T, Milne P. Head injuries to pedal cyclists and the promotion of helmet use in Victoria, Australia. *Accid Anal Prev.* 1988;20:177-185.

7. Thompson RS, Rivara FP, Thompson DC. Prevention of head injury by bicycle helmets: a filed study of efficacy. *AJDC.* 1988;142:386. Abstract.

8. Wasserman RC, Waller JA, Monty M, Emery AB, Robinson DR. Bicyclists, helmets and head injuries: a rider-based study of helmet use and effectiveness. *Am J Public Health.* 1988;78:1220-1221.

9. Selbst SM, Alexander D, Ruddy R. Bicycle-related injuries. *AJDC.* 1987;141:104-144.

10. DiGuiseppi C, Rivara FP, Koepsell T. Bicycle helmet ownership and use among school age children. *AJDC.* 1988;142:386.

11. Krueger RA. *Focus Groups: A Practical Guide for Applied Research.* Beverly Hills, Calif: Sage Publications; 1988.

12. Morgan DL. *Focus Groups as Qualitative Research: Sage University Series on Qualitative Research Methods.* Beverly Hills, Calif: Sage Publications; 1988:16.

13. Elliot & Shanahan Research. *An Exploratory Study of High School Students' Reactions to Bicycle Helmets.* Road Traffic Authority of Victoria, Melbourne, Australia. April 1986. Report No. GR/86/10.

Book Review

Books Received but Not Reviewed

Human Gene Therapy, by Eve K. Nichols, 257 pp, $22.95, Cambridge, Mass, Harvard University Press, 1988.

Human Growth Hormone, by L. E. Underwood, 304 pp, $69.75, New York, NY, Marcel Dekker Inc, 1988.

Hypnosis and Hypnotherapy With Children, by Karen Olness, Gail Gardner, 446 pp, $39, Philadelphia, Pa, WB Saunders Co, 1988.

Informative Morphogenetic Variants in the Newborn Infant, by K. Mehes, 241 pp, $16, Budapest, Hungary, Akademiai Kiado Publishers, 1988.

Lecture Notes on Neonatology, by G. M. Gandy, N. R. C. Robertson, 373 pp, Boston, Mass, Blackwell Scientific Publications, 1988.

Legal Medicine, by American College of Legal Medicine, 646 pp, $85, St Louis, Mo, CV Mosby Co, 1988.

Linear Growth Retardation in Less Developed Countries: Nestle Nutrition Workshop Series, Volume 14, edited by John Waterlow, 313 pp, $40, New York, NY, Raven Press, 1988.

Logan Turner's Diseases of the Nose, Throat and Ear, 10th ed, by A. G. D. Maran, 464 pp, $29.50, Littleton, Mass, PSG Publishing Co, 1988.

Low Protein Cookery for PKU, by Virginia Schuett, 569 pp, $39.50, Minneapolis, Minn, University of Wisconsin Press, 1988.

A Manual of Normal Neonatal Care, by N. R. C. Roberton, 251 pp, $7.95, England, Edward Arnold, 1988.

Medicaid and Pediatric Primary Care, by J Perloff, P Kletke, K Neckerman, 104 pp, $30, Baltimore, Md, The Johns Hopkins Press, 1987.

The Merck Manual of Diagnosis and Therapy, edited by R. Berkow, 2732 pp, $21.50, Rahway, NJ, Merck Co, 1987.

Neonatology: Basic Management, On-Call Problems, Diseases, Drugs, by T. L. Gomella, M. D. Cunningham, 428 pp, $19.95, East Norwalk, Conn, Appleton and Lange, 1988.

Neurology for Non-Neurologists, by W. C. Wiederholt, 356 pp, $39.50, Philadelphia, Pa, WB Saunders Co, 1988.

The New Child Protection Team Handbook, by D. C. Bross, M. R. Lenherr, D. A. Rosenberg, R. D. Krugman, and B. D. Schmitt, 636 pp, $60, New York, NY, Garland Publishers Inc, 1988.

The New Fertility and Conception (The Essential Guide for Childless Couples), by J. Stangel, 286 pp, $8.95, New York, NY, NAL Books, 1988.

No More Hysterectomies, by V. Hufnagel, S. Golant, 330 pp, $18.95, New York, NY, NAL Books, 1988.

Nutritional Support for Sick Children, edited by R. DiToro, 150 pp, $39.50, New York, NY, S Karger AG, 1988.

The Onset of Labor: Cellular and Integrative Mechanisms, by D. McNellis, J. R. G. Challis, P. C. Macdonald, P. W. Nathanielsz, 408 pp, $57.50, Ithaca, NY, Perinatology Press, 1988.

Orphan Drugs, by K. Anderson, L. Anderson, 253 pp, $14.95, Los Angeles, Calif, The Body Press, 1988.

The Parent-Child Connection, by A. Rincover, 200 pp, $12.95, New York, NY, Random House Books of Canada, 1988.

A Parent's Guide to Heart Disorders, by James Moller, W. Neal, W. Hoffman, 163 pp, $14.95, Minneapolis, Minn, University of Wisconsin Press, 1988.

A Parent's Guide to Spina Bifida, by Beth-Ann Bloom, E. Seljeskog, 104 pp, $14.95, Minneapolis, Minn, University of Wisconsin Press, 1988.

Pathogenesis and Immunity in Pertussis, A. C. Wardlaw, and R. Parton, 506 pp, New York, NY, John Wiley & Sons Inc, 1988.

Pediatric Behavioral Neurology: Clinical Principles, by C. Njiokiktjien, 395 pp, $130, Amsterdam, the Netherlands, Suyi Publications, 1988.

Pediatric Gastroenterology, Volumes I and II, edited by E. Lebenthal, 232 pp, $62, Philadelphia, Pa, WB Saunders Co, 1988.

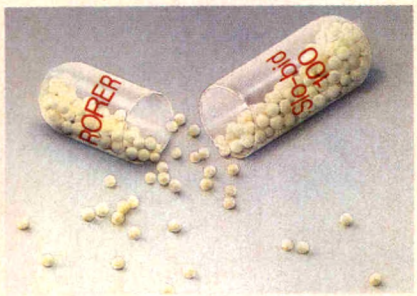
The Pediatric Clinics of North America, edited by S. Kaplan, 244 pp, Philadelphia, Pa, WB Saunders Co, 1988.

The Pediatric Clinics of North America: The Leukemias, D. Poplack, 289 pp, Philadelphia, Pa, WB Saunders Co, 1988.

The Pediatric Drug Handbook, by W. Benitz, D. Tatro, $19.50, Chicago, Ill, Year Book Medical Publishers Inc, 1988.

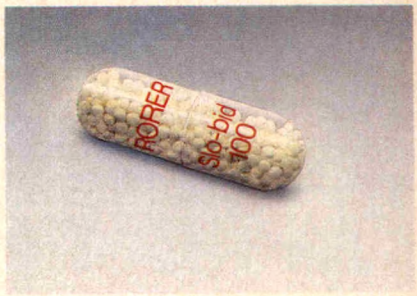
Greater Dosing Flexibility... **NEW Slo-bid™ 75 mg and 125 mg**

Growing up on a steady theophylline is an open-and-shut case



Sprinkled

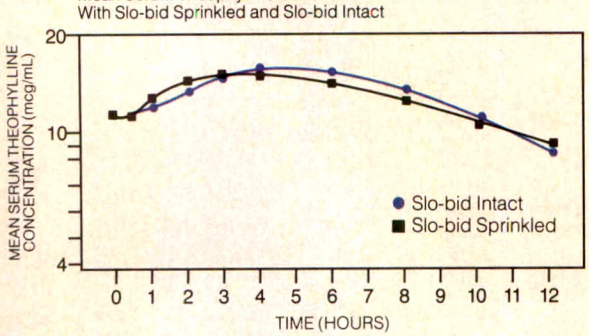
Intact



Changing your patients from sprinkled to solid theophylline administration shouldn't mean changing their serum levels as well. With Slo-bid, you won't change a thing when your younger asthma patients are ready to switch to intact administration.

Slo-bid maintains steady theophylline levels when switching from sprinkled to solid administration[1]

Mean Serum Theophylline Concentration in 14 Children Dosed With Slo-bid Sprinkled and Slo-bid Intact



Switching from Slo-bid sprinkled to Slo-bid intact causes virtually no change in serum levels. Since the release system doesn't change, theophylline performance with both forms is identical. There's no need to restabilize your patients when they switch to taking capsules. In addition, capsules are the dosage form more patients prefer to take.[2]

Keep your patients' theophylline levels steady. Start and stay with Slo-bid. It's the perfect theophylline system for asthma patients to grow up with.

References: 1. Saccar CL, Gawchik S, Spitzer I, et al: Steady-state evaluation of sustained-release theophylline administered in applesauce in asthmatic children. *Immunol Allergy Pract* 1987;9:462-466. 2. Consumer attitudes toward solid forms of medication. Capsugel, Division of Warner-Lambert Company, March 1983.

In Asthma and Bronchitis

Slo-bid™

(theophylline, anhydrous)

Nothing beats our system

From the makers of **Azmacort™** (triamcinolone acetonide)

Please see next page for brief summary of prescribing information.

©1989 Rorer Pharmaceutical Corporation Printed in U.S.A.

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

Slo-bid™

(theophylline, anhydrous)
50 mg, 75 mg, 100 mg, 125 mg, 200 mg, and 300 mg

Gyrocaps®
Timed-Release Capsules

BRIEF SUMMARY

DESCRIPTION: Slo-bid™ Gyrocaps® contain 50 mg, 75 mg, 100 mg, 125 mg, 200 mg, or 300 mg theophylline, anhydrous in the form of long-acting beads within a dye-free hard gelatin capsule and are intended for oral administration. Slo-bid Gyrocaps can be administered with a 12-hour dosing interval for a majority of patients and a 24-hour dosing interval for selected patients (see DOSAGE AND ADMINISTRATION section in full prescribing information for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchitis and emphysema.

CONTRAINDICATIONS: Slo-bid is contraindicated in individuals who have shown hypersensitivity to any of the components of this product. It is also contraindicated in patients with active peptic ulcer disease and in individuals with underlying seizure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20 μg/mL are rarely found after appropriate administration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced *for any reason*, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identifiable groups: 1) patients with impaired renal or liver function; 2) patients over 55 years of age, particularly males and those with chronic lung disease; 3) those with cardiac failure from any cause; 4) patients with sustained high fever; 5) neonates and infants under 1 year of age; and 6) those patients taking certain drugs (see PRECAUTIONS, Drug Interactions). Frequently, such patients have markedly prolonged theophylline serum levels following discontinuation of the drug.

Reduction of dosage and laboratory monitoring is especially appropriate in the above individuals.

Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent during maintenance therapy, they are often associated with serum concentrations above 20 μg/mL. Stated differently, *serious toxicity is not reliably preceded by less severe side effects.* A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and further investigation.

Studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline half-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other xanthine preparations. Use with caution in patients with hypoxemia, hypertension or with a history of peptic ulcer. Theophylline may occasionally act as a local irritant to the GI tract, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 μg/mL.

Information for Patients:
The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The patient should alert the physician if symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

Laboratory Test: Serum levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for toxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the morning dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Drug Interactions:
Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic bronchodilators. In addition, the following drug interactions have been demonstrated:

Theophylline with:	
Allopurinol (high dose)	Increased serum theophylline levels
Cimetidine	Increased serum theophylline levels
Erythromycin, Troleandomycin	Increased serum theophylline levels
Lithium carbonate	Increased renal excretion of lithium
Oral contraceptives	Increased serum theophylline levels
Phenytoin	Decreased theophylline and phenytoin serum levels
Rifampin	Decreased serum theophylline levels

Drug-Food: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk, 2 fried eggs, 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fat) may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (see CLINICAL PHARMACOLOGY, Pharmacokinetics). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromatography and immunoassay techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intraperitoneally in doses up to 30 times the maximum daily human oral dose.

Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C — Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline is distributed into breast milk and may cause irritability or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness of Slo-bid Gyrocaps administered:

1. Every 24 hours in children under 12 years of age, have not been established.
2. Every 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea.

Central Nervous System: headaches, irritability, restlessness, insomnia, reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea

Renal: potentiation of diuresis.

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the reach of children.

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

50 mg — Clear (cap) and opaque white (body) capsule with 50 printed in red
75 mg — Opaque white (cap) and clear (body) capsule with 75 printed in red
100 mg — Clear capsule with 100 printed in red
125 mg — Opaque white (cap) and opaque white (body) capsule with 125 printed in red
200 mg — Opaque white (cap) and clear (body) capsule with 200 printed in red
300 mg — Opaque white capsule with 300 printed in red

Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0057-99) and in unit dose 10 x 10 (NDC 0075-0057-62), Slo-bid Gyrocaps 75 mg are available in bottles of 100 (NDC 0075-1075-00), bottles of 1000 (NDC 0075-1075-99) and in unit dose 10 x 10 (NDC 0075-0057-62), Slo-bid Gyrocaps 100 mg are available in bottles of 100 (NDC 0075-0100-00), bottles of 1000 (NDC 0075-0100-99) and in unit dose 10 x 10 (NDC 0075-0100-62), Slo-bid Gyrocaps 125 mg are available in bottles of 100 (NDC 0075-1125-00), bottles of 1000 (NDC 0075-1125-99) and in unit dose 10 x 10 (NDC 0075-1125-62), Slo-bid Gyrocaps 200 mg are available in bottles of 100 (NDC 0075-0200-00), bottles of 1000 (NDC 0075-0200-99) and in unit dose 10 x 10 (NDC 0075-0200-62), and Slo-bid Gyrocaps 300 mg are available in bottles of 100 (NDC 0075-0300-00), bottles of 1000 (NDC 0075-0300-99) and in unit dose 10 x 10 (NDC 0075-0300-62), and are manufactured by:

RORER PHARMACEUTICALS
a division of
RORER PHARMACEUTICAL CORPORATION
Fort Washington, PA, U.S.A. 19034

The Department of Pediatrics, University of Kansas Medical Center is seeking a full-time board eligible/certified neonatologist in an unqualified tenure track in the Section of Neonatology. Position available July 1, 1989. The candidate will join four full-time neonatologists. The individual should have a commitment to clinical teaching, research and regionalization of perinatal health services. Opportunities to develop both basic and clinical research are available. Rank and salary will be commensurate with experience. Interested and qualified applications should send their curriculum vitae to:

Allen Erenberg, M.D.
Professor and Chairman
Department of Pediatrics
University of Kansas
Medical Center
Kansas City, Kansas 66103

An Equal Opportunity Employer

NEONATOLOGIST

New Hanover Memorial Hospital, located in beautiful, historic, oceanside Wilmington, North Carolina is seeking a board certified or board eligible neonatologist to join team of three. New Hanover Memorial Hospital is a 500 bed major referral hospital for southeastern North Carolina with graduate medical education programs affiliated with the University of North Carolina School of Medicine. Candidate will be eligible for academic appointment at UNC School of Medicine. Academic appointment and salary dependent on training and experience. Please submit curriculum vitae and references to:

Chairman,
Search Committee in Neonatology
Area Health Education Center
New Hanover Memorial Hospital
2131 South 17th Street
Wilmington, North Carolina 28402

The University of North Carolina at Chapel Hill is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

Radiological Cases of the Month

Ronald E. Bokulic, DO; Robert C. Beckerman, MD; Denise Mulvihill, MD (*Contributors*);
Beverly P. Wood, MD (*Section Editor*)

A 22-year-old man with cystic fibrosis (CF) developed tachypnea, fever (temperature, 38.4°C), increased cough, and dyspnea. He also complained of a sore throat, generalized myalgias and arthralgias, diaphoresis, and chills. He was treated with nebulized tobramycin sulfate and oral ciprofloxacin hydrochloride. Bilateral wrist swelling and aching had begun 3 weeks prior to his respiratory symptoms. Because his pulmonary symptoms did not improve with outpatient therapy, the patient was admitted to the hospital.

His vital signs on admission were a temperature of 36.8°C, a heart rate of 148 beats per minute, a respiratory rate of 28/min, and a blood pressure of 131/61 mm Hg. The physical examination revealed a barrel chest, diffuse crackles on auscultation, and severe clubbing of the digits. There was bilateral nontender swelling and deformity of the wrist (Fig 1).

The laboratory results showed a white blood cell count of 10.7×10^9/L with 0.59 segmented neutrophils, 0.24 band cells, 0.13 lymphocytes, and 0.04 mononuclear cells. The erythrocyte sedimentation rate was 82 mm/h; the serum rheumatoid factor value and antinuclear antibody titer were normal, and the results of the blood cultures were negative. The patient's sputum culture yielded *Pseudomonas aeruginosa* (a mucoid and nonmucoid strain) and *Serratia marcescens.*

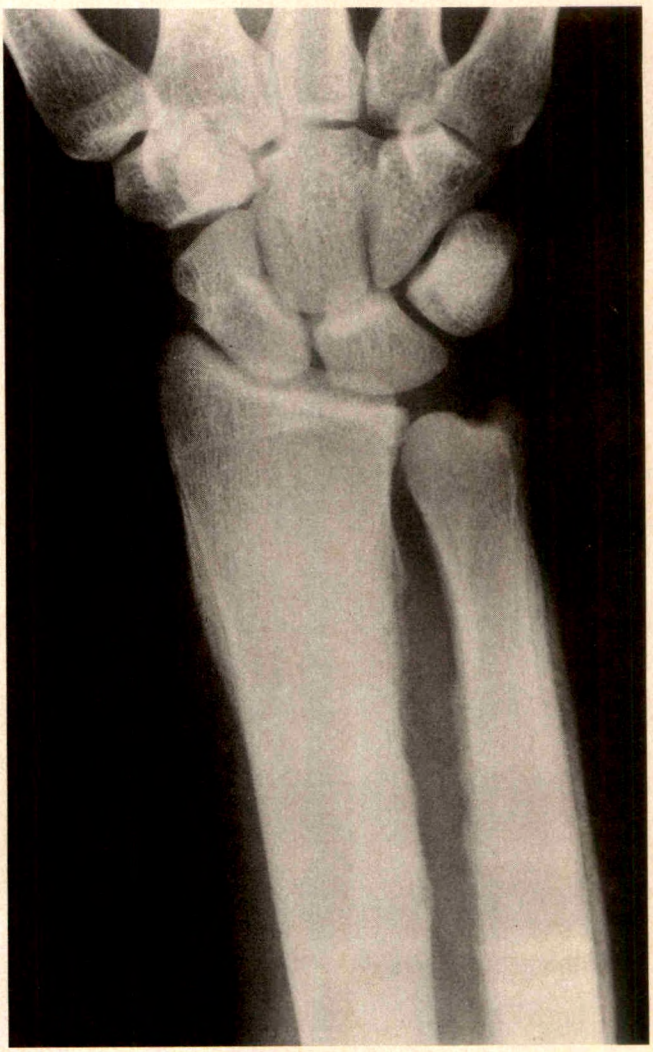


Figure 1.

Accepted for publication October 20, 1988.

Contributed from the Departments of Pediatric Pulmonology (Drs Bokulic and Beckerman) and Pediatric Radiology (Dr Mulvihill), Tulane University School of Medicine, New Orleans, La.

Reprint requests to Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Denouement and Discussion

Hypertrophic Pulmonary Osteoarthropathy

Fig 1.—Admission roentgenogram of the wrist.

Fig 2.—Irregular nodular periosteal new bone proliferation in the distal radius and ulna (arrows).

Fig 3.—Laminated periosteal new bone formation in the distal tibia (arrow).

Patients with acute pulmonary exacerbation of CF may present with diaphoresis, chills, digital clubbing, and arthritis. The roentgenographic abnormality of hypertrophic pulmonary osteoarthropathy (HPO) is notable in our case, producing arthritic symptoms.[1] Cystic fibrosis differs from other described pulmonary causes of HPO because it is typified by bronchiectasis and persistent colonization with *Pseudomonas*. The characteristic observations in HPO include periarticular demineralization, digital clubbing, and joint swelling. Digital clubbing and HPO occur independently of each other.[2] Evidence supporting this fact is the large number of patients with CF who have digital clubbing but no HPO.

Irregular, heavy periosteal new bone formation is the characteristic roentgenographic finding of HPO. The number of affected bones, the distribution, and the extent of involvement are directly related to the duration of the pulmonary disease.[3] In disease of short duration, the periostitis results in thin layers of new bone along the distal diaphysis of the long tubular bones (Figs 2 and 3). As the disease progresses, progressive laminated layers appear and become more sclerotic. Advanced cases, as in the patient described herein, show irregular dense nodular bony proliferation merging with the cortical surface and involving most of the length of the shaft. The bone changes are usually symmetric. The tibia and fibula are the bones most commonly involved, followed by the femur, the radius, and the ulna. In long-standing cases, virtually all the long tubular bones are affected.

Hypertrophic pulmonary osteoarthropathy was first described in 1889 by Marie and Bamberger, who saw an association between hypertrophic osteoarthropathy and chronic intrathoracic infection with bronchiectasis.[4] Although HPO has been associated with a variety of pulmonary diseases, bronchogenic carcinoma accounts for 80% of the cases. Few cases of HPO have been reported in children or adults with CF.[2,5] However, one group of investigators estimates that as many as 15% of patients with CF may develop HPO.[6] The pathophysiology of HPO is postulated to reflect neurohumoral mediation of overgrowth of vascular connective tissue of the long bones.[7]

Our patient was treated with ceftazidime, tobramycin, and ibuprofen with gradual resolution of his pulmonary symptoms and wrist swelling. Symptoms of HPO may resolve with treatment of the underlying pulmonary disorder.[6] Therapy includes resection of causative lung lesions or use of antibiotics. Anti-inflammatory agents are only effective against pain.

Figure 2.

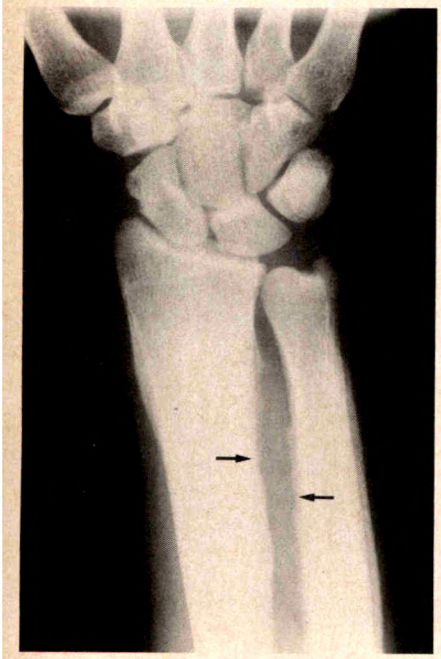
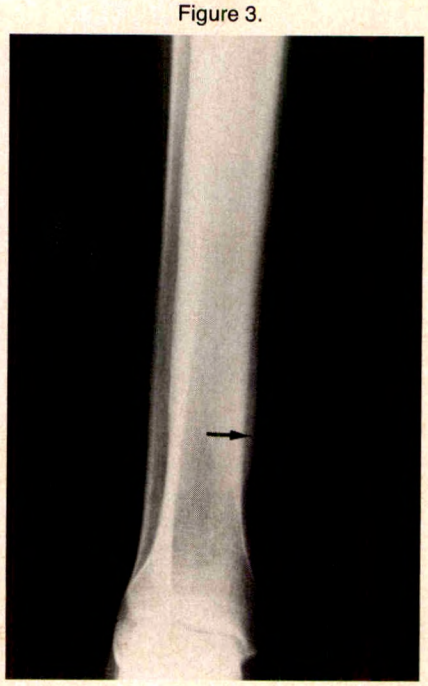


Figure 3.



References

1. Hammarsten JF, O'Leary J. The features and significance of hypertrophic osteoarthropathy. *Arch Intern Med*. 1957;99:431-441.
2. Grossman H, Denning CR, Baker DH. Hypertrophic osteoarthropathy in cystic fibrosis. *AJDC*. 1964;107:1-6.
3. Pineda CJ, Martinez-Lavin M, Goobar JE, Satoris DJ, Clopton P, Resnick D. Periostitis in hypertrophic osteoarthropathy: relationship to disease duration. *Radiology*. 1987;148:773-778.
4. Doyle L. Hypertrophic osteoarthropathy: four early reports by British authors (1889-97). *Thorax*. 1987;42:561-564.
5. Matthay MA, Matthay RA, Mills DM, Lakshminarayan S, Cotton E. Hypertrophic osteoarthropathy in adults with cystic fibrosis. *Thorax*. 1976;31:572-575.
6. Cohen AM, Yulish BS, Wasser KB, Vignos PJ, Jones PK, Sorin SB. Evaluation of pulmonary hypertrophic osteoarthropathy in cystic fibrosis. *AJDC*. 1986;140:74-77.
7. Holling HE, Brodey RS. Pulmonary hypertrophic osteoarthropathy. *JAMA*. 1961;178:977-982.

Gretchen S. Crary, MD; Barbara A. Burke, MD; Bennett A. Alford, MD;
René P. du Cret, MD (*Contributors*); Beverly P. Wood, MD (*Section Editor*)

A 5-year-old girl was admitted to the hospital with lethargy and increasing jaundice. At age 18 months, she had undergone an orthotopic liver transplantation for extrahepatic biliary atresia and had subsequently developed chronic graft rejection. Other medical problems included nutritional deficiency, renal dysfunction, episodes of gastrointestinal hemorrhage, seizures, anemia secondary to chloramphenicol toxicity, developmental delay, and hypoxemia.

Accepted for publication Aug 31, 1988.

Contributed from the Departments of Laboratory Medicine and Pathology (Drs Crary and Burke) and Radiology (Drs Alford and du Cret), University of Minnesota, Minneapolis.

Reprint requests to the Department of Radiology, PO Box 648, University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642 (Dr Wood).

Physical examination revealed a dehydrated, lethargic, jaundiced, and cushingoid-appearing girl who was small for her age. Her weight and height were 13.7 kg and 93 cm, respectively. On auscultation, breath sounds were harsh but there were no rales or rhonchi. She developed persistent hypoxemia and her arterial oxygen saturations ranged from 80% to 90%. Significant pertinent laboratory findings included a total serum bilirubin level of 482 μmol/L, a direct bilirubin level of 314 μmol/L, an aspartate aminotransferase level of 1890 U/L, an alanine aminotransferase level of 652 U/L, an alkaline phosphatase level of 6470 U/L, and a blood ammonia nitrogen level of 90.0 μmol/L.

The patient's chest roentgenogram (Fig 1) and whole-body technetium Tc 99m–labeled aggregated albumin radionuclide scan (Fig 2) are shown.

Figure 1.

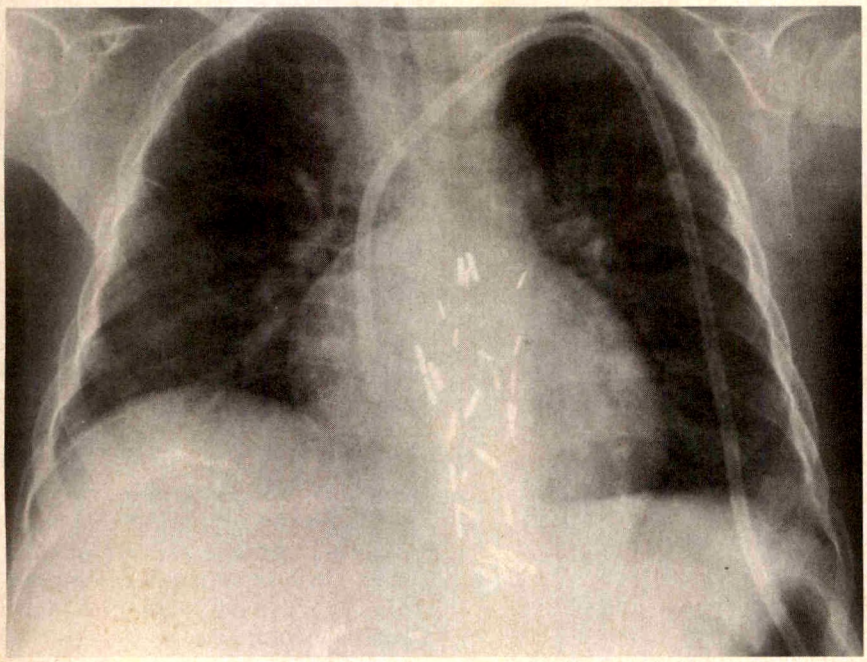
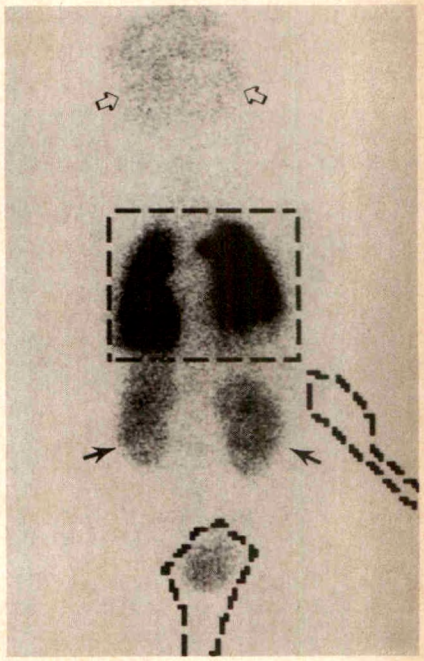


Figure 2.



Denouement and Discussion

Pulmonary Arteriovenous Shunting in a Child With Cirrhosis of the Liver

Fig 1.—Posteroanterior chest roentgenogram showing diffuse bilateral bronchial wall thickening and linear parenchymal opacities.

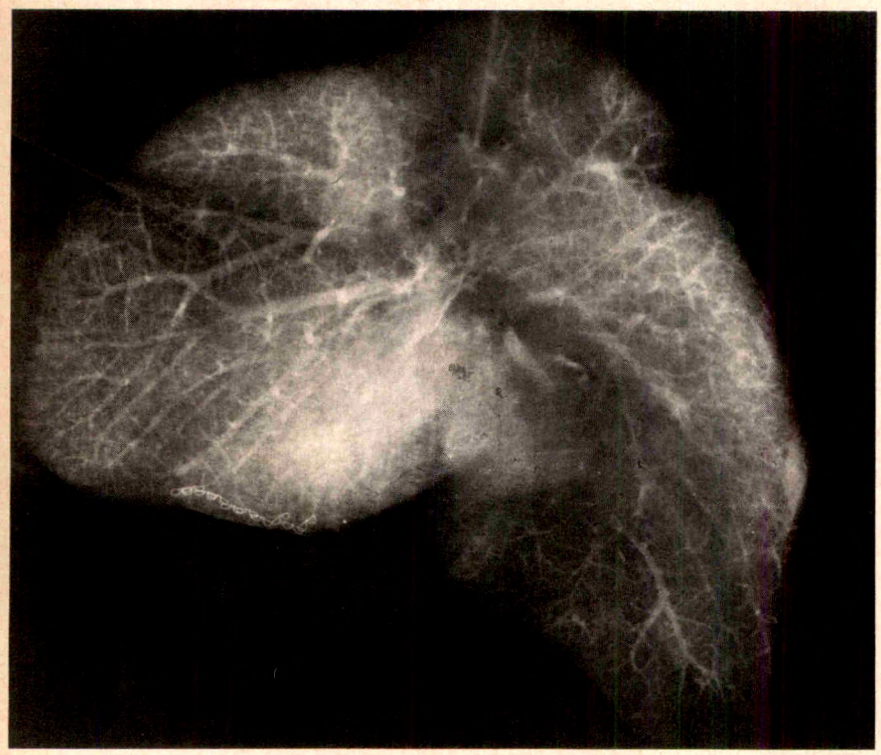
Fig 2.—Whole-body technetium Tc 99m–labeled aggregated albumin scan showing normal accumulation of tracer within lung (enclosed within rectangle) and abnormally increased extrapulmonary sites of activity including brain (open arrows) and kidneys (closed arrows). Extrapulmonary sites of activity accounted for 40% of injected tracer distribution.

Fig 3.—Postmortem right pulmonary arteriogram demonstrating normal vascular arborization with no large venous structures visualized.

Fig 4.—Most branches of pulmonary artery contained injected barium and some showed intimal thickening as well. Communication between one such artery and thin-walled vein is shown (arrowhead). Note granular barium particles in lumen of vein (arrow) (elastic stain, ×20).

The chest roentgenogram showed diffuse bilateral bronchial wall thickening and linear interstitial parenchymal opacities. These had increased over a two-year period. The whole-body technetium-labeled aggregated albumin scan showed right-to-left shunting. In this technique the size of 90% of the particles of albumin is 15 to 90 μm, with an average size of 20 to 40 μm. None of the particles is larger than 150 μm. Immediately following injection, more than 80% of the particles should be trapped in the pulmonary alveolar capillary bed. The accumulation of technetium in the extrapulmonary circulation indicates the presence of arteriovenous (A-V) pulmonary shunting.

Figure 3.



The patient continued to do poorly and died of metabolic encephalopathy one month later. At the time of the autopsy, the pulmonary artery was injected with barium sulfate suspension, and a fluoroscopic examination of the lungs yielded no evidence of large-size right-to-left shunting (Fig 3). However, histopathologic examination of the injected lung showed the presence of A-V shunts (Fig 4), acute bronchopneumonia with mucous plugging, and diffuse alveolar damage. Other autopsy findings included micronodular hepatic cirrhosis with cholestasis and chronic hepatic rejection.

Hepatic cirrhosis is associated with multiple pulmonary abnormalities, including arterial hypoxemia with hemoglobin desaturation and hyperventilation. Oxygen desaturation in patients with cirrhosis may be explained by the following vascular abnormalities: intrapulmonary shunts, portopulmonary shunts, pleural shunting through adhesions, pulmonary hypertension, hypoxic vasoconstriction, and ventilation-perfusion mismatch.[1]

Figure 4.

Intrapulmonary shunting in a child with cirrhosis was first demonstrated by vinyl acetate injection of postmortem pulmonary arteries by Rydell and Hoffbauer in 1956.[2] No A-V shunts were demonstrable using routine methods, but widespread small pulmonary A-V fistulas were identified when plastic casts of the pulmonary vessels were examined. The fistulas were thought to be the result of opening of normal anatomic shunts that are present but not usually patent.[2,3] Such intrapulmonary shunts explain the arterial desaturation and the failure to reverse the desaturation with oxygen therapy. The cause of these shunts remains enigmatic but is related to the presence of hepatic cirrhosis.

Clinically, intrapulmonary shunting is the most important mechanism of severe hypoxemia in patients with cirrhosis. In most cases, the oxygen desaturation is not striking and can be detected only by sensitive methods. In some patients the shunts may produce large alveolar-arterial oxygen pressure gradients that correspond to shunt volume of 20% of cardiac output. Severe shunting may lead to increased cardiac output to meet increased peripheral oxygen demands. Shunting does not appear to be associated with abnormal liver functions test results, ascites, splenomegaly, portal or pulmonary hypertension, or digital clubbing.[4] Portopulmonary shunting probably does not contribute significantly to arterial desaturation; however, pulmonary arterial hypertension may do so.

Premortem quantification of these shunts may be achieved by whole-body radionuclide scanning or contrast two-dimensional echocardiography with intravenous injection of saline or indocyanine dye. These methods may reveal shunts that are not detectable by conventional angiography and have potential value in posttreatment follow-up.[5] Postmortem methods include infusions of vinyl acetate into the pulmonary vasculature[2] and injection of pulmonary arteries with barium sulfate suspension. It is difficult to demonstrate anatomic shunts by traditional histopathologic study. Pulmonary A-V shunts are irreversible even with liver transplantation.[4]

References

1. Martini GA, Baltzer G, Arndt H: Some aspects of circulatory disturbances in cirrhosis of the liver. *Prog Liver Dis* 1972;4:231-250.
2. Rydell R, Hoffbauer FW: Multiple pulmonary arteriovenous fistulas in juvenile cirrhosis. *Am J Med* 1956;21:450-460.
3. Tobin CE, Zariquiey MO: Arteriovenous shunts in the human lung. *Proc Soc Exp Biol Med* 1950;75:827-829
4. Krowka MJ: Pulmonary aspects of chronic liver disease and liver transplantation. *Mayo Clin Proc* 1985;60:407-418.
5. Bank ER, Thrall JH, Dantzker DR: Radionuclide demonstration of intrapulmonary shunting in cirrhosis. *AJR* 1983;140:967-969.

The Editors welcome contributions to PICTURE OF THE MONTH *and* RADIOLOGICAL CASE OF THE MONTH. *Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.*

THE SHAPE OF THINGS TO COME

Available soon
from Lederle Laboratories

SUPRAX®
cefixime/Lederle

© 1989 Lederle Laboratories
7502-9

Lederle
LEDERLE LABORATORIES
A Division of American Cyanamid Company
Wayne, New Jersey 07470

"OUCH"

For "minor league" injuries, there's a better choice than aspirin

When your 6- to 14-year-old patients need pain relief for minor injuries, Junior Strength TYLENOL® acetaminophen should be your first choice. Clinical studies have proven TYLENOL® to be every bit as effective as aspirin for pain relief,[1] with a superior safety profile.[2] Together with the recommended regimen of rest, ice, compression, and elevation, it's the better choice than aspirin for the pain of minor self-limiting injuries.[3]

Junior Strength TYLENOL® can also help reduce underdosing because children need only half as many 160 mg caplets as 80 mg chewables. They're coated for easier swallowing, too.

So next time a junior patient says "Ouch!", recommend local therapy for the inflammation, and make your first choice Junior Strength TYLENOL® acetaminophen for the pain.

References: 1. Cooper SA: *Arch Intern Med* 1981;141:282–285. **2.** Aspirin or paracetamol? *Lancet* 1981;II:287–289. **3.** Senior RJ: *J Adolesc Health Care* 1986;7(suppl to No. 6):24S–30S.

JUNIOR STRENGTH

TYLENOL®

160 mg acetaminophen

COATED CAPLETS

First choice for pain relief in the 6–14 year old

© McN, 1988

McNeil Consumer Products Company
Fort Washington, PA 19034

McNEIL

Because many little hearts are destined for a big problem...

Fatty streaks in the aortas of 3-year-olds Fatty streaks have been found even in the aortas of 3-year-olds. Aortic fatty streaks have been strongly related to both total- and LDL-cholesterol levels and inversely to the HDL/LDL+VLDL ratio. Expert advice suggests that a rational approach to the prevention of CVD should begin early in life.[1]

SMA® maintains high levels of cardio-protective HDL Wyeth's SMA, with a lipid profile virtually identical to mother's milk, provides infants with HDL-cholesterol plasma levels that closely approximate those found in breast-fed infants. And, like breast milk, SMA has more than twice the level of monounsaturates than the other two leading formulas. High levels of monounsaturates have been associated with higher levels of cardio-protective HDL.[2] Start them early...and start them right... with SMA.

References: 1. Newman WP III, *et al:* Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. *N Engl J Med 314*:138-144, 1986. **2.** Mattson FH, Grundy SM: Comparison of effects of dietary saturated, monounsaturated and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. *J Lipid Res 26*:194-202, 1985.

S·M·A™
Infant Formula

A first step in good cardiovascular nutrition

Important Notice. Breast milk is best for babies. Infant formula is intended to replace or supplement breast milk when breast-feeding is not possible or is insufficient, or when mothers elect not to breast-feed.
Good maternal nutrition is important for the preparation and maintenance of breast-feeding. Extensive or prolonged use of partial bottle-feeding, before breast-feeding has been well established, could make breast-feeding difficult to maintain. A decision not to breast-feed could be difficult to reverse.
Professional advice should be followed on the need for and proper method of use of infant formula and on all matters of infant feeding. Infant formula should always be prepared and used as directed. Unnecessary or improper use of infant formula could present a health hazard. Social and financial implications should be considered when selecting the method of infant feeding.

WYETH AYERST™

©1987, Wyeth-Ayerst Laboratories.